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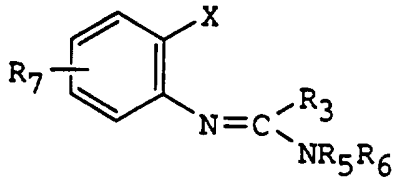
(57) Abstract



(I)

Method for treatment and/or prevention of cerebral and/or cardiac ischaemia, convulsion and/or sickle cell anaemia wherein a therapeutically effective amount of a compound (I) or salt thereof is administered to a mammal in need thereof with an acceptable diluent or carrier, wherein X is H, nitro, cyano, halo, optionally substituted phenyl, alkyl or $-(CH_2)_n NR_1R_2$ wherein R_1 and R_2 are optionally substituted aliphatic group, cycloalkyl, or together with their nitrogen atom form a ring; R_3 is alkyl, cycloalkyl, guanidine or amine (both optionally N-substituted); R_5 is H or optionally substituted aliphatic group; R_6 is H, or phenyl, cycloalkyl or aliphatic group (each optionally substituted); or R_3 and R_5 form a ring; or R_3 and R_5 form a ring containing 2 nitrogen atoms; or R_5 and R_6 form a ring; and R_7 represents H, N-containing ring, or optional substituents; some of which compounds are novel.

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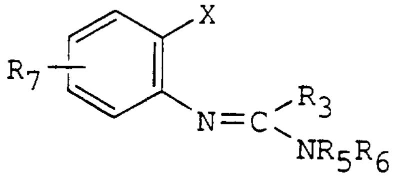
USE OF SUBSTITUTED PHENYLAMIDINE AND PHENYLGUANIDINE COMPOUNDS FOR THE TREATMENT OF CEREBRAL AND CARDIAC ISCHAEMIA, CONVULSION AND SICKLE CELL ANAEMIA

This invention relates to a method for the treatment of cerebral and/or cardiac ischaemia, convulsion and sickle cell anaemia.

According to the present invention there is provided a method for the treatment and/or prevention of cerebral and/or cardiac ischaemia, convulsion and/or sickle cell anaemia in which a therapeutically effective amount of a compound of formula I

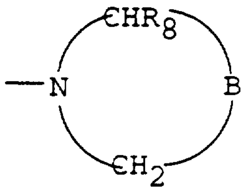


I

or a pharmaceutically acceptable salt thereof is administered to a mammal in need of such treatment in conjunction with a pharmaceutically acceptable diluent or carrier,

in which X is H, nitro, cyano, halo, phenyl (optionally substituted by halo and/or alkyl and/or alkoxy containing 1 to 3 carbon atoms or alkanoyl containing 2 to 4 carbon atoms, or a group of formula $S(O)_mR'$ wherein m is 0 or 1 or 2 and R' is an alkyl group containing 1 to 3 carbon atoms), an alkyl group containing 1 to 4 carbon atoms or a group of formula $-(CH_2)_n NR_1R_2$

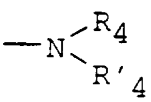
in which n is 0 or 1 and R_1 and R_2, which are the same or different, are (a) an aliphatic group containing 1 to 3 carbon atoms, said aliphatic group being optionally substituted by methoxy (b) a cycloalkyl group containing 3 to 7 carbon atoms or (c) R_1 and R_2 together with the nitrogen atom to which they are attached form an optionally substituted heterocyclic ring of formula II



II

in which R_8 represents H or an alkyl group containing 1 to 3 carbon atoms and B represents an alkylene group of 2 to 4 carbon atoms optionally interrupted by oxygen, sulphur, sulphinyl or nitrogen optionally substituted by an alkyl group containing 1 to 3 carbon atoms, said alkylene group being optionally substituted by one or more alkyl groups containing 1 to 3 carbon atoms or the substituents on two adjacent carbon atoms of the alkylene group form a benzene ring or B represents an alkenylene group of 3 carbon atoms;

R_3 is a straight or branched alkyl group containing 1 to 7 carbon atoms or a guanidine group (optionally N-substituted in both the 1 and 3 positions with one or two alkyl groups containing 1 to 3 carbon atoms) or R_3 is a cycloalkyl group containing 3 to 7 carbon atoms or a group of formula III



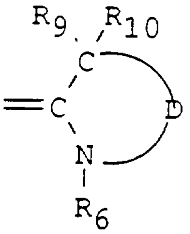
$-N(R_4)(R'_4)$ III

in which R_4 and R'_4, which are the same or different, are H or an alkyl group containing 1 to 4 carbon atoms;

R_5 is H or a straight or branched aliphatic group of 1 to 4 carbon atoms, said aliphatic group being optionally substituted by methoxy;

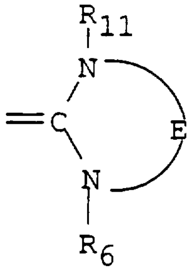
R_6 is (a) H, or phenyl (optionally substituted by halo and/or alkyl and/or alkoxy containing 1 to 4 carbon atoms) (b) a straight or branched aliphatic group of 1 to 6 carbon atoms optionally substituted by hydroxy or an acylated derivative thereof, by an alkoxy group containing 1 to 3 carbon atoms, by an alkylthio group containing 1 to 3 carbon atoms, by an optionally alkylated amino group, by a carbocyclic group containing 3 to 7 carbon atoms, by pyridyl or by cyano or (c) a cycloalkyl ring containing 3 to 7 carbon atoms and optionally substituted by hydroxy;

or the group R_3 and the group R_5 together with the carbon and nitrogen atoms to which they are attached form a heterocyclic ring of formula IV



in which R_6 is as hereinbefore defined, R_9 and R_{10}, which are the same or different, are H or an alkyl group of 1 to 4 carbon atoms optionally substituted by methoxy and D is an oxyethylene group in which the oxygen atom is bonded to the carbon atom carrying the groups R_9 and R_{10} or an alkylene group of 2 to 5 carbon atoms optionally substituted by one or more alkyl groups of 1 to 3 carbon atoms;

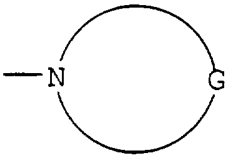
or the group R_3 and the group R_5 together with the carbon and nitrogen atoms to which they are attached form a heterocyclic ring of formula V



V

in which R_6 is as hereinbefore described, R_{11} is H or an alkyl group containing 1 or 2 carbon atoms, and E is an alkylene group of 2 to 4 carbon atoms optionally substituted by one or more alkyl groups containing 1 to 3 carbon atoms;

or R_5 and R_6 together with the nitrogen atom to which they are attached form a heterocyclic ring of formula VI



VI

in which G is an alkylene or alkenylene group of 4 to 6 carbon atoms optionally interrupted by oxygen, sulphur, sulphinyl, sulphonyl, or nitrogen said nitrogen being optionally substituted by (a) a carbocyclic ring containing 3 to 7 carbon atoms (b) a methylsulphonyl group or (c) an alkyl group containing 1 to 3 carbon atoms and optionally substituted by hydroxy or an alkoxy group containing 1 to 3 carbon atoms; said alkylene group being optionally substituted by (a) one or more alkyl groups containing 1 to 3 carbon atoms and optionally substituted by hydroxy, (b) by one or more hydroxy groups or an ester thereof, (c) by one or more alkoxy groups, (d) by oxo or a derivative thereof (eg an oxime or oxime ether), (e) by dimethylcarbamoyl or (f) by one or more groups of formula $S(O)_pR''$ in which p = 0 or 1 or 2 and R'' is an alkyl group containing 1 to 3 carbon atoms; and

R_7 represents H or a group of formula II above or one or more optional substituents selected from halo, alkyl groups containing 1 to 4 carbon atoms optionally substituted by methylthio, alkoxy groups containing 1 to 3 carbon atoms, alkylthio groups containing 1 to 3 carbon atoms, alkylsulphinyl groups containing 1 to 3 carbon atoms, alkylsulphonyl groups containing 1 to 3 carbon atoms, alkoxycarbonyl groups containing a total of 2 or 3 carbon atoms, trifluoromethyl or cyano.

In preferred compounds of formula I in which X is a group of formula $-(CH_2)_nNR_1R_2$ in which n = 0; R_1 and R_2, which may be the same or different, are selected from (a) alkyl groups of 1 to 3 carbon atoms optionally substituted by methoxy (b) allyl groups or (c) cyclohexyl groups. In particularly preferred such compounds of formula I in which n = 0, R_1 and R_2 are both alkyl, allyl or 2-methoxyethyl or R_1 is methyl and R_2 is 2-methoxyethyl or cyclohexyl. In especially preferred such compounds of formula I in which n = 0, the group NR_1R_2 is dimethylamino, diethylamino, diallylamino, (2-methoxyethyl)methylamino, cyclohexylmethylamino or bis(2-methoxyethyl)amino.

In preferred compounds of formula I in which X is a group of formula $-(CH_2)_nNR_1R_2$ in which n = 0 and in which the group NR_1R_2 is a heterocyclic ring represented by formula II, R_8 represents H or methyl and B represents a group selected from $-(CH_2)_2-$, $-CHMeCH_2-$, o-phenylene, $-(CH_2)_3-$, $-CH_2CHMeCH_2-$, $-(CH_2)_4-$, $-CH_2OCH_2-$, $-CHMeOCHMe-$, $-CH_2SCH_2-$, $-CH_2S(O)CH_2-$, $-CH_2NMeCH_2-$ or $-CH=CHCH_2-$. In especially preferred such compounds of formula I in which n = 0 and the group NR_1R_2 is a group of formula II, the group NR_1R_2 is 1-pyrrolidinyl, 2-methyl-1-pyrrolidinyl, piperidino, 4-methylpiperidino, 1-hexahydroazepinyl, morpholino, 2,6-dimethylmorpholino, thiamorpholino, thiamorpholino-1-oxide, 2-isoindolinyl, 4-methyl-1-piperazinyl or 1-(1,2,5,6-tetrahydro)pyridyl. In preferred such compounds of formula I in which n = 1, the group NR_1R_2 is morpholino or thiamorpholino.

In compounds of formula I in which R_3 is an alkyl group, the group R_3 preferably contains 1 to 5 carbon atoms (e.g. methyl, ethyl, propyl, isopropyl, butyl, t-butyl or pentyl). In compounds of formula I in which the group R_3 is a cycloalkyl group, the cycloalkyl group is preferably cyclohexyl.

In preferred compounds of formula I in which R_3 is a group of formula III, R_4 and R_4' are H, methyl or ethyl and at least one of R_4 and R'_4 is other than H (for example R_3 is methylamino, dimethylamino or ethylamino).

In preferred compounds of formula I in which the group R_5 does not form part of a heterocyclic ring, the group R_5 is H or an alkyl group containing 1 to 3 carbon atoms (eg methyl or ethyl) optionally substituted by methoxy (eg R_5 is methoxyethyl) or allyl.

In preferred compounds of formula I in which X is phenyl (or substituted phenyl) and the groups R_5 and R_6 do not form part of a heterocyclic ring, the group R_5 is H or an alkyl group containing 1 to 3 carbon atoms (eg methyl or ethyl) and the group R_6 is (a) H, (b) an alkyl group of 1 to 3 carbon atoms (eg ethyl) optionally substituted by methoxy, pyridyl or dimethylamino (eg R_6 is 2-methoxyethyl, 2-pyridylethyl or 2-dimethylaminoethyl) or (c) a phenyl group substituted by hydroxy.

In preferred compounds of formula I, R_6 is H or a straight or branched alkyl group containing 1 to 5 carbon atoms (e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl or pentyl) optionally substituted by hydroxy (e.g. R_6 is 2-hydroxyethyl, 3-hydroxypropyl, 2-hydroxypropyl, 2-hydroxybutyl, 2-hydroxy-2-methylpropyl, or 2,3-dihydroxypropyl), by an acylated derivative of hydroxy such as acetyloxy or benzoyloxy (e.g. R_6 is 2-acetyloxyethyl or 2-benzoyloxyethyl) by methoxy (e.g. R_6 is 2-methoxyethyl), by methylthio (eg R_6 is 2-methylthioethyl), by dimethylamino (e.g. R_6 is 2-dimethylaminoethyl), by phenyl (e.g. R_6 is benzyl or 2-phenylethyl) or by cyano (e.g. R_6 is 2-cyanoethyl) or R_6 is a straight or branched alkylene group containing 3 to 6 carbon atoms (e.g. R_6 is allyl or 2-methyl-allyl).

In preferred compounds of formula I in which R_6 is a cycloalkyl group, R_6 contains 5 or 6 carbon atoms (e.g. R_6 is cyclopentyl or cyclohexyl).

In particularly preferred compounds of formula I in which the groups R_3 and R_5 together with the nitrogen and carbon atoms to which they are attached do not form a heterocyclic ring, the group $-N{=}C(R_3)NR_5R_6$ is:-

acetamidino,
N-methylacetamidino,
N,N-dimethylacetamidino,
N,N-diethylacetamidino,

N-(2-acetyloxyethyl)acetamidino,
N-butylacetamidino,
N-pentylacetamidino,
N-methylpropionamidino,
N,N-dimethylpropionamidino
N-ethylpropionamidino,
butyramidino,
N-methylbutyramidino,
N,N-dimethylbutyramidino,
N-ethylbutyramidino,
isobutyramidino,
N-methylisobutyramidino,
N,N-dimethylisobutyramidino,
valeramidino,
N-methylvaleramidino,
N,N-dimethylvaleramidino,
pivalamidino,
N-methylpivalamidino,
N,N-dimethylpivalamidino,
N-methylcaproamidino
N-methylcyclohexanecarboxamidino,
diaminomethyleneamino,
N-methylguanidino,
N,N-dimethylguanidino,
N,N'-dimethylguanidino,
N-ethylguanidino,
N-butylguanidino,
N-ethyl-N-methylguanidino,
N,N-diethylguanidino,
N,N'-diethylguanidino,
N,N',N'-trimethylguanidino,
1,1,3,3-tetramethylguanidino,
N-ethyl-N'-methylguanidino,
1-ethyl-1,3,3-trimethylguanidino,
1-butyl-1,3,3-trimethylguanidino,
N-methyl-N-propylguanidino,

N-butyl-N-methylguanidino,
N-sec-butyl-N'-methylguanidino,
N-tert-butyl-N'-methylguanidino,
N-isobutyl-N'-methylguanidino,
N-butyl-N'-methylguanidino,
N-butyl-N'-ethylguanidino,
N-methyl-N'-pentylguanidino,
N-cyclopentyl-N'-methylguanidino,
N-(2-methoxyethyl)guanidino,
N-(2-methoxyethyl)-N-methylguanidino,
N-(2-methoxyethyl)-N'-methylguanidino,
N-ethyl-N-(2-methoxyethyl)guanidino,
N,N-bis(2-methoxyethyl)guanidino,
N-methyl-N-(2-methylthioethyl)guanidino,
N-allyl-N-methylguanidino,
N-allyl-N'-methylguanidino,
1-allyl-1,3,3-trimethylguanidino,
N,N-diallylguanidino,

In one group of preferred compounds of formula I in which the groups R_3 and R_5 together with the carbon and nitrogen atoms to which they are attached form a heterocyclic ring of formula IV, R_9 and R_{10}, which may be the same or different, are H or alkyl groups containing 1 to 3 carbon atoms (for example methyl, ethyl or isopropyl) optionally substituted by methoxy (eg R_9 and/or R_{10} are methoxyethyl), D is selected from $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-CH_2CMe_2-$ or $-O(CH_2)_2-$ and the group R_6 is preferably H, methyl, ethyl, isopropyl, cyclohexyl, 2-cyanoethyl, 2-acetoxyethyl or 2-methoxyethyl. In particularly preferred compounds of formula I, formula IV represents:-

2-pyrrolidinylidene,
1-methyl-2-pyrrolidinylidene,

3-methyl-2-pyrrolidinylidene,
1-ethyl-2-pyrrolidinylidene,
1-isopropyl-2-pyrrolidinylidene,
1-cyclohexyl-2-pyrrolidinylidene,
1-(2-methoxyethyl)-2-pyrrolidinylidene,
1,3-dimethyl-2-pyrrolidinylidene,
5,5-dimethyl-2-pyrrolidinylidene,
1,3,3-trimethyl-2-pyrrolidinylidene,
1,5,5-trimethyl-2-pyrrolidinylidene,
3-isopropyl-1-methyl-2-pyrrolidinylidene,
1-ethyl-3,3-dimethyl-2-pyrrolidinylidene,
3,3-diethyl-1-methyl-2-pyrrolidinylidene,
2-piperidinylidene,
1-methyl-2-piperidinylidene,
1,3-dimethylpiperidinylidene,
1-ethyl-2-piperidinylidene,
1-isopropyl-2-piperidinylidene,
1-(2-cyanoethyl)-2-piperidinylidene,
1-(2-acetoxyethyl)-2-piperidinylidene,
3-(2-methoxyethyl)-1-methyl-2-piperidinylidene,
2-hexahydroazepinylidene,
1-methyl-2-hexahydroazepinylidene,
2-octahydroazocinylidene or
3-morpholinylidene.

In a second group of preferred compounds of formula I in which the groups R_3 and R_5 together with the carbon and nitrogen atoms to which they are attached form a heterocyclic ring of formula V,
E is $-CH_2CH_2-$, $-CMe_2CH_2-$, -CHMeCHMe-, $-(CH_2)_3-$, $CHMeCH_2-$ or $-(CH_2)_4$, R_{11} is H, methyl or ethyl and R_6 is H, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, allyl, 2-methylallyl, 2-hydroxyethyl, 2-acetoxyethyl, 2-benzoyloxyethyl, 2-methoxyethyl, cyclohexyl, benzyl, phenethyl, 3-hydroxypropyl, 2-hydroxypropyl, 2-hydroxy-2-methylpropyl, 2-hydroxy-

butyl, 2,3-dihydroxypropyl or 2-dimethylaminoethyl. In particularly preferred compounds of formula I, formula V represents:-

2-imidazolidinylidene,
1-methyl-2-imidazolidinylidene,
4-methyl-2-imidazolidinylidene,
4,4-dimethyl-2-imidazolidinylidene,
4,5-dimethyl-2-imidazolidinylidene,
1-ethyl-2-imidazolidinylidene,
1-propyl-2-imidazolidinylidene,
1-isopropyl-2-imidazolidinylidene,
1-(n-butyl)-2-imidazolidinylidene,
1-isobutyl-2-imidazolidinylidene,
1-pentyl-2-imidazolidinylidene,
1-allyl-2-imidazolidinylidene,
1-(2-methylallyl)-2-imidazolidinylidene,
1-(2-hydroxyethyl)-2-imidazolidinylidene,
1-(2-hydroxyethyl)-3-methyl-2-imidazolidinylidene,
1-(2-acetoxyethyl)-2-imidazolidinylidene,
1-(2-benzoyloxyethyl)-2-imidazolidinylidene,
1-(2-benzoyloxyethyl)-3-methyl-2-imidazolidinylidene,
4,5-dimethyl-1-(2-hydroxyethyl)-2-imidazolidinylidene,
1-(2-methoxyethyl)-2-imidazolidinylidene,
1-(2-methoxyethyl)-3-methyl-2-imidazolidinylidene,
1-cyclohexyl-2-imidazolidinylidene,
1-benzyl-2-imidazolidinylidene,
1-(2-phenylethyl)-2-imidazolidinylidene,
1-(2-dimethylaminoethyl)-2-imidazolidinylidene,
1-(3-hydroxypropyl)-2-imidazolidinylidene,
1-(2-hydroxypropyl)-2-imidazolidinylidene,
1-(2-hydroxy-2-methylpropyl)-2-imidazolidinylidene,
1-(2-hydroxybutyl)-2-imidazolidinylidene,
1-(2,3-dihydroxypropyl)-2-imidazolidinylidene,
1,3-dimethyl-2-imidazolidinylidene,
1,3-diethyl-2-imidazolidinylidene,

1-ethyl-3-methyl-2-imidazolidinylidene,
1-butyl-3-methyl-2-imidazolidinylidene,
1-isopropyl-4,4-dimethyl-2-imidazolidinylidene,
1-methyl-2-perhydropyrimidinylidene or
1,3-diazacycloheptan-2-ylidene.

In preferred compounds of formula I in which R_5 and R_6 together with the nitrogen atom to which they are attached form a heterocyclic ring of formula VI, G represents a group selected from

$-(CH_2)_4-$,
$-(CH_2)_5-$,
$-CH_2-CH=CH-(CH_2)_2-$,
$-(CH_2)_2O(CH_2)_2-$,
$-(CH_2)_2OCHMeCH_2-$
$-CMe_2CH_2O(CH_2)_2-$
$-(CH_2)_2S(CH_2)_2-$,
$-(CH_2)_2SO(CH_2)_2-$,
$-(CH_2)_2SO_2(CH_2)_2-$,
$-(CH_2)_2NMe(CH_2)_2-$,
$-(CH_2)_2NEt(CH_2)_2-$
$-(CH_2)_2N(SO_2Me)(CH_2)_2-$,
$-(CH_2)_2N(CH_2CH_2OH)(CH_2)_2-$,
$-(CH_2)_2CHMe(CH_2)_2-$,
$-CH_2CH(OH)(CH_2)_2-$,
$-CH_2CH(OH)(CH_2)_3-$,
$-CH_2CH(CH_2OH)(CH_2)_3-$,
$-(CH_2)_2CH(CH_2OH)(CH_2)_2-$,
$-(CH_2)_2CH(OH)(CH_2)_2-$,
$-(CH_2)_2C(OH)(Me)(CH_2)_2-$,
$-(CH_2)_2CH(OMe)(CH_2)_2-$,
$-CH_2CH(OMe)(CH_2)_3-$,
$-(CH_2)_2CH(CONMe_2)(CH_2)_2-$
$-(CH_2)_2CO(CH_2)_2-$
$-(CH_2)_2C=NOH(CH_2)_2-$,

$-(CH_2)_2C{=}NOMe(CH_2)_2-$,
$-CH_2CHMeOCHMeCH_2-$

In particularly preferred compounds of formula I in which R_5 and R_6 together form a heterocyclic ring of formula VI, the group NR_5R_6 is 1-pyrrolidinyl, 2,6-dimethylmorpholino, 3-hydroxy-1-pyrrolidinyl, piperidino, 1,2,5,6-tetrahydropyridyl, 4-methylpiperidino, 3-hydroxypiperidino, 4-hydroxypiperidino, 4-hydroxy-4-methylpiperidino, 3-methoxypiperidino, 4-methoxypiperidino, 3-hydroxymethylpiperidino, 4-hydroxymethylpiperidino, 4-dimethylcarbamoylpiperidino, 4-piperidinon-1-yl, 4-piperidinon-1-yl oxime, 4-piperidinon-1-yl oxime-O-methyl ether, morpholino, 2-methylmorpholino, 3,3-dimethylmorpholino, thiomorpholino, thiomorpholino-1-oxide, thiomorpholino-1,1-dioxide, 4-methyl-1-piperazinyl, 4-ethyl-1-piperazinyl, 4-(2-hydroxyethyl)-1-piperazinyl, 4-methyl-sulphonyl-1-piperazinyl.

In particularly preferred compounds of formula I the group $-N{=}C(R_3)NR_5R_6$ is:-

N-methylpivalamidino,
cyclohexanecarboxamidino,
N,N-dimethylguanidino,
N,N'-dimethylguanidino,
N-methyl-N-(2-pyridylethyl)guanidino,
N-ethyl-N-(2-methoxyethyl)guanidino,
N-methyl-N-(2-dimethylaminoethyl)guanidino,
N-(4-hydroxyphenyl)-N-methylguanidino,
N,N-(3-oxapentamethylene)guanidino,
N,N-(2-methyl-3-oxapentamethylene)guanidino,
N,N-(1,1-dimethyl-3-oxapentamethylene)guanidino,
N,N-(3-thiapentamethylene)guanidino,
N,N-(3-thiapentamethylene)guanidino S-oxide,

N,N-(3-thiapentamethylene)guanidino S,S-dioxide,
N,N-(3-methyl-3-azapentamethylene)guanidino,
N,N-(3-ethyl-3-azapentamethylene)guanidino,
N,N-[3-(2-hydroxyethyl)-3-azapentamethylene]-guanidino,
N,N-(3-methylsulphonyl-3-azapentamethylene)-guanidino,
N,N-(2-hydroxytetramethylene)guanidino,
N,N-pentamethyleneguanidino,
N,N-(2-pentenylene)guanidino,
N,N-(3-methylpentamethylene)guanidino,
N,N-(2-hydroxypentamethylene)guanidino,
N,N-(3-hydroxypentamethylene)guanidino,
N,N-(3-hydroxy-3-methylpentamethylene)guanidino,
N,N-(2-hydroxymethylpentamethylene)guanidino,
N,N-(3-hydroxymethylpentamethylene)guanidino,
N,N-(3-dimethylcarbamoylpentamethylene)guanidino,
N,N-(2-methoxypentamethylene)guanidino,
N,N-(3-methoxypentamethylene)guanidino,
N,N-(3-oxopentamethylene)guanidino,
N,N-(3-hydroxyiminopentamethylene)guanidino,
N,N-(3-methoxyiminopentamethylene)guanidino,
N,N-(2,4-dimethyl-3-oxopentamethylene)guanidino,
N-methyl-N′,N′-tetramethylene)guanidino,
N,N-(1,1-dimethylpentamethylene)guanidino.

In preferred compounds of formula I, R_7 represents H or one or more substituents (preferably one or two substituents) selected from fluoro, chloro, methyl, ethyl, isobutyl, methylthiomethyl, methoxy, methoxycarbonyl, methylthio, methylsulphinyl, methylsulphonyl, trifluoromethyl or cyano.

Specific compounds of formula I wherein X is not phenyl or substituted phenyl are

4-[2-(2-piperidinylideneamino)phenyl]morpholine
4-[2-(1-methyl-2-piperidinylideneamino)phenyl]-morpholine
4-[2-(1-ethyl-2-piperidinylideneamino)phenyl]-morpholine
4-[2-(1-isopropyl-2-piperidinylideneamino)phenyl]-morpholine
4-[2-(2-hexahydroazepinylideneamino)phenyl]morpholine
4-[2-(1-methyl-2-hexahydroazepinylideneamino)phenyl]-morpholine
4-[2-(2-octahydroazocinylideneamino)phenyl]morpholine
4-[2-(2-pyrrolidinylideneamino)phenyl]morpholine
4-[2-(1-methyl-2-pyrrolidinylideneamino)phenyl]-morpholine
4-[2-(1,3-dimethyl-2-pyrrolidinylideneamino)-phenyl]morpholine
4-[2-(1,3,3-trimethyl-2-pyrrolidinylideneamino)-phenyl]morpholine
4-[2-(1-ethyl-2-pyrrolidinylideneamino)phenyl]-morpholine
4-{2-[1-(2-methoxyethyl)-2-pyrrolidinylideneamino]-phenyl}morpholine
4-[2-(1-cyclohexyl-2-pyrrolidinylideneamino)phenyl]-morpholine
4-[2-(3,3-dimethyl-1-ethyl-2-pyrrolidinylideneamino)phenyl]morpholine
4-[2-(3,3-diethyl-1-methyl-2-pyrrolidinylideneamino)-phenyl]morpholine
4-[2-(3-isopropyl-1-methyl-2-pyrrolidinylideneamino)phenyl]morpholine
4-[2-(1,3-dimethyl-2-piperidinylideneamino)phenyl]-morpholine
4-[3-methyl-2-(2-piperidinylideneamino)phenyl]-morpholine
4-[3-methyl-2-(1-methyl-2-piperidinylideneamino) phenyl]morpholine

4-[4-methyl-2-(2-piperidinylideneamino)phenyl]-morpholine

4-[4-methyl-2-(1-methyl-2-piperidinylideneamino)-phenyl]morpholine

4-[5-methyl-2-(2-piperidinylideneamino)phenyl]-morpholine

4-[6-methyl-2-(2-piperidinylideneamino)phenyl]-morpholine

4-[4-ethyl-2-(2-piperidinylideneamino)phenyl] morpholine

4-[3-chloro-2-(2-piperidinylideneamino)phenyl]-morpholine

4-[4-chloro-2-(2-piperidinylideneamino)phenyl]-morpholine

4-[4-chloro-2-(1-methyl-2-piperidinylideneamino) phenyl]morpholine

4-[5-chloro-2-(2-piperidinylideneamino)phenyl]-morpholine

4-[6-chloro-2-(2-piperidinylideneamino)phenyl]-morpholine

4-[4-fluoro-2-(2-piperidinylideneamino)phenyl]-morpholine

4-[4-fluoro-2-(1-methyl-2-piperidinylideneamino)-phenyl]morpholine

4-[4-methoxy-2-(2-piperidinylideneamino)phenyl]-morpholine

4-[4-methoxycarbonyl-2-(2-piperidinylideneamino) phenyl]-morpholine

4-[4-methylsulphonyl-2-(2-piperidinylideneamino) phenyl]morpholine

4-{2-[1-(2-acetoxyethyl)-2-piperidinylideneamino]-phenyl}morpholine

4-{2-[1-methyl-3-(2-methoxyethyl)-2-piperidinylidene-amino]phenyl}morpholine

4-[2-(3-methyl-2-pyrrolidinylideneamino)phenyl]-morpholine

N-methyl-N'-(2-morpholinophenyl)acetamidine
N-(2-morpholinophenyl)-N'-propylacetamidine
N-(n-butyl)-N'-(2-morpholinophenyl)acetamidine
N-(n-pentyl)-N'-(2-morpholinophenyl)acetamidine
N-(2-acetoxyethyl)-N'-(2-morpholinophenyl)-acetamidine
N,N-dimethyl-N'-(2-morpholinophenyl)acetamidine
N,N-diethyl-N'-(2-morpholinophenyl)acetamidine
N-methyl-N'-(2-morpholinophenyl)propionamidine
N-ethyl-N'-(2-morpholinophenyl)propionamidine
N,N-dimethyl-N'-(2-morpholinophenyl)propionamidine
N-methyl-N'-(2-morpholinophenyl)butyramidine
N-ethyl-N'-(2-morpholinophenyl)butyramidine
N,N-dimethyl-N'-(2-morpholinophenyl)butyramidine
N-methyl-N'-(2-morpholinophenyl)-2-methyl-propionamidine
N,N-dimethyl-N'-(2-morpholinophenyl)-2-methyl-propionamidine
N-methyl-N'-(2-morpholinophenyl)valeramidine
N,N-dimethyl-N'-(2-morpholinophenyl)valeramidine
N-methyl-N'-(2-morpholinophenyl)pivalamidine
N,N-dimethyl-N'-(2-morpholinophenyl)pivalamidine
N-methyl-N'-(2-morpholinophenyl)hexanamidine
N-methyl-N'-[2-(1-pyrrolidinyl)phenyl]butyramidine
N-methyl-N'-[2-(1-pyrrolidinyl)phenyl]pivalamidine
N-methyl-N'-(2-morpholinophenyl)cyclohexane carboxamidine
N-methyl-N'-(2-piperidinophenyl)pivalamidine
1-[2-(2-piperidinylideneamino)phenyl]pyrrolidine
1-[2-(1-methyl-2-piperidinylideneamino)phenyl]-pyrrolidine
1-[2-(1-ethyl-2-piperidinylideneamino)phenyl]-pyrrolidine
1-[4-chloro-2-(1-methyl-2-piperidinylideneamino)-phenyl]pyrrolidine
1-[3-methyl-2-(1-methyl-2-piperidinylideneamino)-

phenyl]pyrrolidine
1-[2-(1-methyl-2-pyrrolidinylideneamino)phenyl]-pyrrolidine
1-[2-(1,3-dimethyl-2-pyrrolidinylideneamino)phenyl]-pyrrolidine
1-[2-(1-methyl-2-hexahydroazepinylideneamino)phenyl]-pyrrolidine
1-[4-methyl-2-(2-piperidinylideneamino)phenyl]-pyrrolidine
1-[4-chloro-2-(2-piperidinylideneamino)phenyl]-pyrrolidine
1-[3-methyl-2-(2-piperidinylideneamino)phenyl]-pyrrolidine
1-[6-methyl-2-(2-piperidinylideneamino)phenyl]-pyrrolidine
4-[2-(2-piperidinylideneamino)phenyl]thiamorpholine
1-[2-(2-piperidinylideneamino)phenyl]piperidine
1-[2-(1-methyl-2-piperidinylideneamino)phenyl]-piperidine
1-[2-(2-piperidinylideneamino)phenyl]hexahydroazepine
2,6-dimethyl-4-[2-(2-piperidinylideneamino)phenyl]-morpholine
4-methyl-1-[2-(2-piperidinylideneamino)phenyl]-piperidine
1-[2-(2-piperidinylideneamino)phenyl]-1,2,5,6-tetrahydropyridine
2-methyl-1-[2-(2-piperidinylideneamino)phenyl]-pyrrolidine
2-[2-(2-piperidinylideneamino)phenyl]isoindoline
4-[2-(1-methyl-2-piperidinylideneamino)phenyl]-thiamorpholine
4-[4-methyl-2-(2-piperidinylideneamino)-phenyl]thiamorpholine
N-(2-methoxyethyl)-N-[2-(2-piperidinylideneamino)-phenyl]methylamine
N-[2-(2-piperidinylideneamino)phenyl]dimethylamine

N-[2-(2-piperidinylideneamino)phenyl]diallylamine

N-cyclohexyl-N-[2-(2-piperidinylideneamino)phenyl]-methylamine

N-[2-(2-piperidinylidineaminophenyl)-bis-(2-methoxy-ethyl)amine

4-[2-(1,3,3-trimethyl-2-pyrrolidinylidineamino)-phenyl]thiamorpholine

1-[2-(1,3,3-trimethyl-2-pyrrolidinylidineamino)-phenyl]piperidine

1-[2-(1,3,3-trimethyl-2-pyrrolidinylidineamino)phenyl]-4-methylpiperazine

1-[2-(1,3,3-trimethyl-2-pyrrolidinylidineamino)-phenyl]pyrrolidine

4-[4-methyl-2-(1,3,3-trimethyl-2-pyrrolidinylidene-amino)phenyl]morpholine

1-[2-(1-methyl-2-pyrrolidinylideneamino)phenyl]-piperidine

1-[2-(1,3-dimethyl-2-pyrrolidinylideneamino)phenyl]-piperidine

4-[2-(5,5-dimethyl-2-pyrrolidinylideneamino)phenyl]-morpholine

4-[1,5,5-trimethyl-2-pyrrolidinylideneamino)phenyl]-morpholine

N-[2-(1,3,3-trimethyl-2-pyrrolidinylideneamino)phenyl]-bis-(2-methoxyethyl)amine

N-(2-morpholinophenyl)acetamidine

N-(5-methyl-2-morpholinophenyl)acetamidine

N-(2-morpholinophenyl)propionamidine

N-(2-morpholinophenyl)butyramidine

N-(2-morpholinophenyl)isobutyramidine

N-(5-methylthio-2-morpholinophenyl)isobutyramidine

N-(5-fluoro-2-morpholinophenyl)isobutyramidine

N-(2-morpholinophenyl)valeramidine

N-(2-morpholinophenyl)pivalamidine

4-(2-[1-(cyanoethyl)-2-piperidinylideneamino]phenyl)-morpholine

4-[2-(3-morpholinylideneamino)phenyl]morpholine
4-[2-(2-piperidinylideneamino)benzyl]morpholine
4-[2-(1-methyl-2-pyrrolidinylideneamino)benzyl]-morpholine
4-[4-chloro-2-(2-piperidinylideneamino)benzyl]-morpholine
4-[2-(1,3,3-trimethyl-2-pyrrolidinylideneamino)-benzyl]morpholine
N-methyl-N'-(2-morpholinomethylphenyl)pivalamidine
4-[2-(1,3-dimethyl-2-imidazolidinylideneamino)phenyl]-morpholine
4-[2-(1,3-dimethyl-2-imidazolidinylideneamino)-4-fluorophenyl]morpholine
4-[2-(1,3-dimethyl-2-imidazolidinylideneamino)-3-methylphenyl]morpholine
4-[2-(1,3-dimethyl-2-imidazolidinylideneamino)-4-methylphenyl]morpholine
4-[2-(1,3-dimethyl-2-imidazolidinylideneamino)-5-methylphenyl]morpholine
4-[4-chloro-2-(1,3-dimethyl-2-imidazolidinylidene-amino)phenyl]morpholine
4-[2-(1,3-dimethyl-2-imidazolidinylideneamino)-4-methoxyphenyl]morpholine
4-[4,5-dimethoxy-2-(1,3-dimethyl-2-imidazolidinylidene-amino)phenyl]morpholine
1-[2-(1,3-dimethyl-2-imidazolidinylideneamino)phenyl]-pyrrolidine
1-[2-(1,3-dimethyl-2-imidazolidinylideneamino)-3-methylphenyl]pyrrolidine
1-[2-(1,3-dimethyl-2-imidazolidinylideneamino)phenyl]-piperidine
4-[2-(1,3-dimethyl-2-imidazolidinylideneamino)phenyl]-thiamorpholine
2,6-dimethyl-4-[2-(1,3-dimethyl-2-imidazolidinylidene-amino)phenyl]morpholine
N-[2-(1,3-dimethyl-2-imidazolidinylideneamino)phenyl]-

diethylamine

1-[2-(1,3-dimethyl-2-imidazolidinylideneamino)phenyl]-2-methylpyrrolidine

4-[3-chloro-2-(1,3-dimethyl-2-imidazolidinylideneamino)phenyl]morpholine

1-[2-(1,3-dimethyl-2-imidazolidinylideneamino)-4-methylphenyl]pyrrolidine

N-[2-(1,3-dimethyl-2-imidazolidinylideneamino)phenyl]-bis-(2-methoxyethyl)amine

4-[2-(1,3-diethyl-2-imidazolidinylideneamino)phenyl]-morpholine

4-[2-(1,3-dimethyl-2-imidazolidinylideneamino)-6-methylphenyl]pyrrolidine

4-[2-(1-ethyl-3-methyl-2-imidazolidinylideneamino)-phenyl]morpholine

4-[2-(1-n-butyl-3-methyl-2-imidazolidinylideneamino)-phenyl]morpholine

4-{2-[1-(2-benzoyloxyethyl)-3-methyl-2-imidazolinylideneamino]phenyl}morpholine

2-(2-morpholinophenyl)-1,1,3,3-tetramethylguanidine

1-ethyl-2-(2-morpholinophenyl)-1,3,3-trimethyl-guanidine

1-allyl-2-(2-morpholinophenyl)-1,3,3-trimethyl-guanidine

1-n-butyl-2-(2-morpholinophenyl)-1,3,3-trimethyl-guanidine

1-pentyl-2-(2-morpholinophenyl)-1,3,3-trimethyl-guanidine

4-{2-[1-methyl-3-(2-methoxyethyl)-2-imidazolidinylideneamino]phenyl}morpholine

4-{2-[1-methyl-3-(2-hydroxyethyl)-2-imidazolidinylideneamino]phenyl}morpholine

N,N-dimethyl-N'-(2-morpholinophenyl)morpholine-4-carboxamidine

N,N-dimethyl-N'-(2-morpholinophenyl)piperidine-1-carboxamidine

4-[2-(1,3-dimethyl-2-imidazolidinylideneamino) phenyl]thiamorpholine-1-oxide
4-[2-(2-imidazolidinylideneamino)phenyl]morpholine
4-[2-(1-methyl-2-imidazolidinylideneamino)phenyl]-morpholine
4-[2-(1-ethyl-2-imidazolidinylideneamino)phenyl]-morpholine
4-[2-(1-n-propyl-2-imidazolidinylideneamino)phenyl]-morpholine
4-[2-(1-isopropyl-2-imidazolidinylideneamino)phenyl]-morpholine
4-[2-(1-n-butyl-2-imidazolidinylideneamino)phenyl]-morpholine
4-[2-(1-isobutyl-2-imidazolidinylamino)phenyl]-morpholine
4-[2-(1-pentyl-2-imidazolidinylamino)phenyl]-morpholine
4-[2-(1-allyl-2-imidazolidinylideneamino)phenyl]-
4-(2-[1-(2-hydroxyethyl)-2-imidazolidinylideneamino] phenyl)morpholine
4-{2-[1-(2-hydroxyethyl)-2-imidazolidinylideneamino]-3-methylphenyl}morpholine
4-{2-[1-(2-methoxyethyl)-2-imidazolidinylideneamino] phenyl}morpholine
4-[2-(1-cyclohexyl-2-imidazolidinylideneamino)phenyl]-morpholine
4-[2-(1-benzyl-2-imidazolidinylideneamino)phenyl]-morpholine
4-{2-[1-(2-phenylethyl)-2-imidazolidinylideneamino]-phenyl}morpholine
4-{2-[1-(2-dimethylaminoethyl)-2-imidazolidinylidene-amino]phenyl}morpholine
4-{2-[1-(2,3-dihydroxypropyl)-2-imidazolidinylidene-amino]phenyl}morpholine
4-{2-[1-(2-methylallyl)-2-imidazolidinylideneamino]-phenyl}morpholine

N-[2-(1-methyl-2-imidazolidinylideneamino)phenyl]bis-(2-methoxyethyl)amine

N-{2-[1-(2-hydroxyethyl)-2-imidazolidinylideneamino]-phenyl}bis-(2-methoxyethyl)amine

4-[2-(1-methyl-2-imidazolidinylideneamino)phenyl] thiamorpholine

1-[2-(1-methyl-2-imidazolidinylideneamino)phenyl] pyrrolidine

4-[2-(1-n-butyl-2-imidazolidinylideneamino)phenyl]-thiamorpholine

4-[2-(1-methyl-2-imidazolidinylideneamino)-3-methyl-phenyl]morpholine

4-[2-(1-methyl-2-imidazolidinylideneamino)-4-methyl-phenyl]morpholine

1-{2-[1-(2-hydroxyethyl)-2-imidazolindinylideneamino]-phenyl}pyrrolidine

1-{2-[1-(2-hydroxyethyl)-2-imidazolindinylideneamino]-phenyl}-2-methylpyrrolidine

4-[4-methyl-2-(1-butyl-2-imidazolidinylidene)-phenyl]morpholine

1-[2-(2-imidazolidinylideneamino)phenyl]piperidine

1-[2-(1-methyl-2-imidazolidinylideneamino)phenyl]-piperidine

1-[2-(1-methyl-2-imidazolidinylideneamino)-3-methyl-phenyl]piperidine

4-{2-[1-(2-hydroxyethyl)-2-imidazolidinylidene-amino]phenyl}thiamorpholine

1-{2-[1-(2-hydroxyethyl)-2-imidazolidinylidene-amino]phenyl}piperidine

4-{2-[1-(3-hydroxypropyl)-2-imidazolidinylideneamino]-phenyl}morpholine

4-{2-[1-(2-hydroxypropyl)-2-imidazolidinylideneamino]-phenyl}morpholine

4-{2-[1-(2-hydroxybutyl)-2-imidazolidinylideneamino]-phenyl}morpholine

4-{2-[1-(2-hydroxy-2-methylpropyl)-2-imidazolidinylideneamino]phenyl}morpholine
4-[2-(4-methyl-2-imidazolidinylideneamino)phenyl]-morpholine
4-[2-(4,5-dimethyl-2-imidazolidinylideneamino)phenyl] morpholine
4-{2-[4,5-dimethyl-1-(2-hydroxyethyl)-2-imidazolidinylideneamino]phenyl}morpholine
4-[2-(1-isopropyl-4,4-dimethyl-2-imidazolidinylideneamino)phenyl]morpholine
4-[2-(1-methylperhydropyrimidin-2-ylideneamino)-phenyl]morpholine
2-(2-morpholinophenylimino)-1,3-diazacycloheptane
1,1-dimethyl-2-(2-morpholinophenyl)guanidine
1,3-dimethyl-2-(2-morpholinophenyl)guanidine
1,3,3-trimethyl-2-(2-morpholinophenyl)guanidine
1-ethyl-2-(2-morpholinophenyl)-3-methyl-guanidine
1,3-diethyl-2-(2-morpholinophenyl)guanidine
4-{2-[1-(2-acetyloxyethyl)-2-imidazolidinylideneamino]phenyl}morpholine
4-{2-[1-(2-benzoyloxyethyl)-2-imidazolidinylideneamino]phenyl}morpholine
1-(n-butyl)-2-(2-morpholinophenyl)-3-methyl-guanidine
1-(2-methoxyethyl)-2-(2-piperidinophenyl)guanidine
1-(2-methylthioethyl)-2-(2-morpholinophenyl)guanidine
1-(2-methoxyethyl)-2-(2-morpholinephenyl)guanidine
1-(n-propyl)-2-(2-morpholinophenyl)-3-methylguanidine
1-(2-methoxyethyl)-3-methyl-2-(2-morpholinophenyl) guanidine
1-cyclopentyl-2-(2-morpholinophenyl)-3-methyl-guanidine
N-methyl-N'-(2-morpholinophenyl)pyrrolidine-1-carboxamidine
1-(n-butyl)-2-(2-morpholinophenyl)-3-ethylguanidine

1,3-dimethyl-2-(5-chloro-2-morpholinophenyl)guanidine

1-allyl-2-[2-(1-pyrrolidinyl)phenyl]-3-methylguanidine

1,3-dimethyl-2-(5-methyl-2-morpholinophenyl)-guanidine

4-{2-[1-(2-hydroxyethyl)-2-imidazolidinylideneamino]-4-methylphenyl}morpholine

1-methyl-2-(2-morpholinophenyl)-3-(n-pentyl)guanidine

1-(n-butyl)-2-(5-methyl-2-morpholinophenyl)-3-methylguanidine

1-(n-butyl)-2-(6-methyl-2-morpholinophenyl)-3-methylguanidine

1-(n-butyl)-2-(5-fluoro-2-morpholinophenyl)-3-methylguanidine

1-(n-butyl)-2-(5-methylthio-2-morpholinophenyl)-3-methylguanidine

1-isobutyl-2-(2-morpholinophenyl)-3-methylguanidine

1-sec-butyl-2-(2-morpholinophenyl)-3-methylguanidine

1-tert-butyl-2-(2-morpholinophenyl)-3-methylguanidine

1-allyl-2-(2-morpholinophenyl)-3-methylguanidine

1-(n-butyl)-2-(2-thiamorpholinophenyl)-3-methyl-guanidine

1,1-dimethyl-2-(2-morpholino-5-trifluoromethyl-phenyl)guanidine

1,1-dimethyl-2-(5-cyano-2-morpholinophenyl)guanidine

1,3-di-(n-propyl)-2-(2-morpholinophenyl)guanidine

2-(2-morpholinophenyl)guanidine

1,1-dimethyl-2-(5-methyl-2-morpholinophenyl)guanidine

1,1-dimethyl-2-(6-methyl-2-morpholinophenyl)guanidine

1,1-dimethyl-2-(4-chloro-2-morpholinophenyl)guanidine

1,1-dimethyl-2-(3-chloro-2-morpholinophenyl)guanidine

1,1-dimethyl-2-(5-methoxy-2-morpholinophenyl)guanidine

1,1-dimethyl-2-(5-methylthio-2-morpholinophenyl)-guanidine

1,1-dimethyl-2-(4-methyl-2-morpholinophenyl)guanidine

1,1-dimethyl-2-(5-ethyl-2-morpholinophenyl)guanidine

1,1-dimethyl-2-(5-methylthiomethyl-2-morpholinophenyl)guanidine
1,1-diethyl-2-(2-morpholinophenyl)guanidine
1-(n-butyl)-1-methyl-2-(2-morpholinophenyl)guanidine
1,1-bis(2-methoxyethyl)-2-(2-morpholinophenyl)-guanidine
N-(2-morpholinophenyl)morpholine-4-carboxamidine
N-(2-morpholinophenyl)pyrrolidine-1-carboxamidine
1,1-dimethyl-2-(2-piperidinophenyl)guanidine
1,1-dimethyl-2-[2-(1-pyrrolidinyl)phenyl]guanidine
1,1-dimethyl-2-(2-thiamorpholinophenyl)guanidine
1,1-dimethyl-2-(2-dimethylaminophenyl)guanidine
1,1-dimethyl-2-{2-[N-(2-methoxyethyl)-N-methylamino] phenyl}guanidine
1,1-dimethyl-2-[2-(4-methyl-1-piperazinyl)phenyl] guanidine
N-(2-piperidinophenyl)morpholine-4-carboxamidine
N-(2-piperidinophenyl)piperidine-1-carboxamidine
1,1-dimethyl-2-(5-methoxycarbonyl-2-morpholinophenyl)guanidine
1-methyl-2-(2-morpholinophenyl)guanidine
1-ethyl-2-(2-morpholinophenyl)guanidine
1-butyl-2-(2-morpholinophenyl)guanidine
1-ethyl-1-methyl-2-(2-morpholinophenyl)guanidine
1-methyl-1-(2-methylthioethyl)-2-(2-morpholinophenyl)guanidine
1-(2-methoxyethyl)-1-methyl-2-(2-morpholinophenyl) guanidine
1-allyl-1-methyl-2-(2-morpholinophenyl)guanidine
1-ethyl-1-(2-methoxyethyl)-2-(2-morpholinophenyl) guanidine
1,1-diallyl-2-(2-morpholinophenyl)guanidine
N-(2-morpholinophenyl)-4-methylpiperazine-1-carboxamidine
N-(2-morpholinophenyl)-2,6-dimethylmorpholine-4-carboxamidine

N-(2-morpholinophenyl)thiamorpholine-4-carboxamidine

N-(2-morpholinophenyl)-4-methylpiperidine-1-carboxamidine

N-(2-morpholiniphenyl)thiamorpholine-1-carboxamidine

1,1-dimethyl-2-(5-chloro-2-morpholinophenyl)guanidine

1,1-dimethyl-2-(3-methyl-2-morpholinophenyl)guanidine

1,1-dimethyl-2-(4-methoxy-2-morpholinophenyl)guanidine

1,1-dimethyl-2-(5-isobutyl-2-morpholinophenyl)-guanidine

1,1-dimethyl-2-(5-methylsulphinyl-2-morpholinophenyl)guanidine

4-[2-(1,3-dimethyl-2-imidazolidinylideneamino)-benzyl]morpholine

4-[4-chloro-2-(1,3-dimethyl-2-imidazolidinylideneamino)benzyl]morpholine

N,N-dimethyl-N'-(2-morpholinomethylphenyl)guanidine

N-(2-morpholinomethylphenyl)morpholine-4-carboxamidine

and pharmaceutically acceptable salts thereof.

In preferred compounds of formula I in which X is phenyl or substituted phenyl, X is phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 4-chlorophenyl, 4-methoxyphenyl, 3-methylphenyl, 4-methylphenyl, 3-methylthiophenyl, 3-methanesulphonylphenyl, 4-methanesulphonylphenyl or 4-acetylphenyl.

Specific compounds of formula I wherein X is phenyl or substituted phenyl are:-

2-(2-piperidinylideneamino)biphenyl

2-(1,3-dimethyl-2-imidazolidinylideneamino)-biphenyl

N-(2-biphenylyl)-N'-methylpivalamidine

N-(2-biphenylyl)cyclohexane-1-carboxamidine

2-(1-methyl-2-imidazolidinylideneamino)biphenyl

2-(1-n-butyl-2-imidazolidinylideneamino)biphenyl

2-[1-(2-hydroxyethyl)-2-imidazolidinylideneamino]biphenyl

N-(2-biphenylyl)-N',N"-dimethylguanidine

N-(2-biphenylyl)-N',N'-dimethylguanidine

N-(4-methoxy-2-biphenylyl)-N',N'-dimethylguanidine

N-(2-biphenylyl)morpholine-4-carboxamidine

N-(4-methoxy-2-biphenylyl)morpholine-4-carboxamidine

N-(5-methoxy-2-biphenylyl)piperidine-1-carboxamidine

N-(3'-methyl-2-biphenylyl)piperidine-1-carboxamidine

N-(4'-methanesulphonyl-2-biphenylyl)piperidine-1-carboxamidine

N-(4-methyl-2-biphenylyl)morpholine-4-carboxamidine

N-(5-methoxy-2-biphenylyl)-N',N'-dimethylguanidine

N,N-dimethyl-N'-(5-methylthio-2-biphenylyl)guanidine

N-(4'-acetyl-2-biphenylyl)-N',N'-dimethylguanidine

N,N-dimethyl-N'-(3-methyl-2-biphenylyl)guanidine

N,N-dimethyl-N'-(6-methyl-2-biphenylyl)guanidine

N-(5-fluoro-2-biphenylyl)-N',N'-dimethylguanidine

N-(3'-fluoro-2-biphenylyl)-N',N'-dimethylguanidine

N,N-dimethyl-N'-(3'-methyl-2-biphenylyl)guanidine

N,N-dimethyl-N'-(4'-methanesulphonyl-2-biphenyl)-guanidine

N,N-dimethyl-N'-(4'-methyl-2-biphenylyl)-guanidine

N-(2-biphenylyl)-N'-(4-hydroxyphenyl)-N'-methylguanidine

N,N-dimethyl-N'-(3'-methylthio-2-biphenyl)-guanidine

N-(2-biphenylyl)piperidine-1-carboxamidine

N-(2-biphenylyl)-1,2,5,6-tetrahydropyridine-1-carboxamidine

N-(2-biphenylyl)-4-methylpiperidine-1-carboxamidine

N-(2-biphenylyl)-4-hydroxypiperidine-1-carboxamidine

N-(4-fluoro-2-biphenylyl)-4-hydroxypiperidine-1-carboxamidine

N-(5-fluoro-2-biphenylyl)-4-hydroxypiperidine-1-carboxamidine

N-(3-methyl-2-biphenylyl)-4-hydroxypiperidine-1-carboxamidine

N-(5-methyl-2-biphenylyl)-4-hydroxypiperidine-1-carboxamidine

N-(4-methylthio-2-biphenylyl)-4-hydroxypiperidine-1-carboxamidine

N-(5-methylthio-2-biphenylyl)-4-hydroxypiperidine-1-carboxamidine

N-(2-biphenylyl)-4-methoxypiperidine-1-carboxamidine

N-(2-biphenylyl)-3-methoxypiperidine-1-carboxamidine

N-(2-biphenylyl)-3-hydroxymethylpiperidine-1-carboxamidine

N-(2-biphenylyl)-4-hydroxymethylpiperidine-1-carboxamidine

N-(2-biphenylyl)-4-methoxyiminopiperidine-1-

carboxamidine

N-(2-biphenylyl)-4-hydroxy-4-methylpiperidine-1-carboxamidine

N-(2-biphenylyl)-4-dimethylcarbamoylpiperidine-1-carboxamidine

N-(5-methylthio-2-biphenylyl)morpholine-4-carboxamidine

N-(2-biphenylyl)-2-methylmorpholine-4-carboxamidine

N-(2-biphenylyl)-3,3-dimethylmorpholine-4-carboxamidine

N-(2-biphenylyl)thiomorpholine-4-carboxamidine

N-(2-biphenylyl)thiomorpholine-1,1-dioxide-4-carboxamidine

N-(2-biphenylyl)-3-hydroxypyrrolidine-1-carboxamidine

N-(2-biphenylyl)-4-methylpiperazine-1-carboxamidine

N-(4-fluoro-2-biphenylyl)-4-methylpiperazine-1-carboxamidine

N-(5-fluoro-2-biphenylyl)-4-methylpiperazine-1-carboxamidine

N-(3-methyl-2-biphenylyl)-4-methylpiperazine-1-carboxamidine

N-(5-methyl-2-biphenylyl)-4-methylpiperazine-1-carboxamidine

N-(4-methylthio-2-biphenylyl)-4-methylpiperazine-1-carboxamidine

N-(5-methylthio-2-biphenylyl)-4-methylpiperazine-1-carboxamidine

N-(2-biphenylyl)-4-ethylpiperazine-1-carboxamidine

N-(2-biphenylyl)-4-(2-hydroxyethyl)piperazine-1-carboxamidine

N-(2-biphenylyl)-N'-methyl-N'-[2-(2-pyridyl)-ethyl]guanidine

N-(2-biphenylyl)-N'-ethyl-N'-(2-methoxyethyl)-guanidine

N-(2-biphenylyl)-N'-methyl-N'-(2-dimethylaminoethyl)guanidine

N-(2-biphenylyl)-4-methanesulphonylpiperazine-1-carboxamidine

N-(2-biphenylyl)-4-piperidone-1-carboxamidine

N-(3'-methanesulphonyl-2-biphenylyl)-N',N'-dimethylguanidine

N-(4'-chloro-2-biphenylyl)-N',N'-dimethyl -guanidine

N-(4'-fluoro-2-biphenylyl)-4-hydroxypiperidine-1-carboxamidine

N-(2'-fluoro-2-biphenylyl)-4-methylpiperazine-1-carboxamidine

N-(2'-fluoro-2-biphenylyl)-4-hydroxypiperidine-1-carboxamidine

N-(3'-fluoro-2-biphenylyl)-4-hydroxypiperidine-1-carboxamidine

N-(3'-fluoro-2-biphenylyl)-4-methylpiperazine-1-carboxamidine

N-(2-biphenylyl)-3-hydroxypiperidine-1-carboxamidine

N-(2-biphenylyl)-4-hydroxyiminopiperidine-1-carboxamidine

N-(2-biphenylyl)thiomorpholine-1-oxide-4-carboxamidine

N-(4'-methoxy-2-biphenylyl)-N',N'-dimethyl-guanidine

and pharmaceutically acceptable salts thereof.

One group of preferred compounds of formula I includes compounds of formula I in which n = 0, X is a group of formula $-NR_1R_2$ which is morpholino, thiamorpholino, piperidino or 1-pyrrolidinyl, R_3 is $-NH_2$, R_5 is an aliphatic group containing 1 to 4 carbon atoms (eg methyl, ethyl or allyl), R_6 is an aliphatic group of 1 to 4 carbon atoms optionally substituted by methoxy or methylthio (eg methyl, ethyl, allyl, methoxyethyl or methylthioethyl) or R_5 and R_6 together with the nitrogen atom to which they are attached form a heterocyclic ring of formula VI (e.g. morpholino or thiamorpholino) and R_7 is H, chloro, methyl, ethyl, methylthiomethyl or methylthio.

Specific compounds falling within this one group of preferred compounds include:-
1,1-dimethyl-2-(2-morpholinophenyl)guanidine
1,1-dimethyl-2-(5-chloro-2-morpholinophenyl)guanidine
1,1-dimethyl-2-(5-methyl-2-morpholinophenyl)guanidine
1,1-dimethyl-2-(6-methyl-2-morpholinophenyl)guanidine
1,1-dimethyl-2-(5-ethyl-2-morpholinophenyl)guanidine
1,1-dimethyl-2-(5-methylthiomethyl-2-morpholinophenyl) guanidine
1,1-dimethyl-2-(5-methylthio-2-morpholinophenyl) guanidine
1-ethyl-1-methyl-2-(2-morpholinophenyl)guanidine
1,1-diethyl-2-(2-morpholinophenyl)guanidine
1-(2-methoxyethyl)-1-methyl-2-(2-morpholinophenyl) guanidine
1-methyl-1-(2-methylthioethyl)-2-(2-morpholinophenyl)-guanidine
1,1-dimethyl-2-(2-thiamorpholinophenyl)guanidine
1,1-dimethyl-2-(2-piperidinophenyl)guanidine
1,1-dimethyl-2-[2-(1-pyrrolidinyl)phenyl]guanidine
N-(2-morpholinophenyl)morpholine-4-carboxamidine
N-(2-morpholinophenyl)thiamorpholine-4-carboxamidine

and pharmaceutically acceptable salts thereof.

A second group of preferred compounds of formula I includes compounds of formula I in which n = 0, $-NR_1R_2$

is morpholino or thiamorpholino, R_3 is a group of formula III in which R_4 is an alkyl group containing 1 to 4 carbon atoms (eg methyl) and R_4' is H, R_5 is H, R_6 is an aliphatic group containing 1 to 4 carbon atoms (eg methyl, butyl or -butyl) optionally substituted by methoxy (e.g. R_6 is methoxyethyl) and R_7 is H, fluoro, methyl, methylthio or methylthiomethyl.

Specific compounds falling within this second group of preferred compounds include:-

1-butyl-3-methyl-2-(2-morpholinophenyl)guanidine
1-methyl-3-tert-butyl-2-(2-morpholinophenyl)guanidine
1-methyl-3-tert-butyl-2-(4-fluoro-2-morpholinophenyl) guanidine
1-methyl-3-tert-butyl-2-(4-methyl-2-morpholinophenyl) guanidine
1-methyl-3-tert-butyl-2-(4-methylthio-2-morpholinophenyl)guanidine
1-methyl-3-tert-butyl-2-(4-methylthiomethyl-2-morpholinophenyl)guanidine
1-(2-methoxyethyl)-3-methyl-2-(2-morpholinophenyl) guanidine
1,3-dimethyl-2-(2-thiamorpholinophenyl)guanidine
1-methyl-3-tert-butyl-2-(2-thiamorpholinophenyl) guanidine

and pharmaceutically acceptable salts thereof

A further group of preferred compounds of formula I includes compounds of formula I in which n = 0, $-NR_1R_2$ is morpholino, thiamorpholino, morpholinomethyl or thiamorpholinomethyl, R_3 is an alkyl group of 1 to 4 carbon atoms (eg methyl and t-butyl), R_5 and R_6 are H and R_7 is H, fluoro, methyl, methylthio or methylthiomethyl.

Specific compounds falling within this further group of preferred compounds include:-

N-(2-morpholinophenyl)acetamidine
N-(4-fluoro-2-morpholinophenyl)acetamidine
N-(4-methyl-2-morpholinophenyl)acetamidine
N-(4-methylthio-2-morpholinophenyl)acetamidine
N-(4-methylthiomethyl-2-morpholinophenyl)acetamidine
N-(2-thiamorpholinophenyl)acetamidine
N-(2-morpholinomethylphenyl)acetamidine
N-(2-morpholinophenyl)pivalamidine
N-(2-morpholinomethylphenyl)pivalamidine

and pharmaceutically acceptable salts thereof.

Preferably the compounds are used in the treatment of humans.

The preparation and use of many compounds of formula I, and salts thereof, in the treatment of diabetes is described in European Patent Publication No. 0385038 and in European Patent Publication No. 0536151(WO92/00273) (all in the name of The Boots Company PLC).

The present invention further provides the use of a compound of formula I as defined above in the manufacture of a medicament for the treatment and/or prevention of cerebral and/or cardiac ischaemia.

The present invention further provides the use of a compound of formula I as defined above in the manufacture of a medicament for the treatment and/or prevention of sickle cell anaemia.

The present invention further provides the use of a compound of formula I as defined above in the manufacture of a medicament for use as an anticonvulsant.

The present invention further provides the use of a compound of formula I in the manufacture of a medicament for use as a neuroprotective agent.

There is further provided a pharmaceutical composition for the treatment and/or prevention of cerebral and/or cardiac ischaemia comprising a therapeutically effective amount of a compound of formula I as defined above in conjunction with a pharmaceutically acceptable diluent or carrier.

The present invention further provides a pharmaceutical composition for the treatment and/or prevention of sickle cell anaemia comprising a therapeutically effective amount of a compound of formula I as defined above in conjunction with a pharmaceutically acceptable diluent or carrier.

The present invention further provides a pharmaceutical composition for use as an anticonvulsant comprising a therapeutically effective amount of a compound of formula I as defined above in conjunction with a pharmaceutically acceptable diluent or carrier.

Whilst not wishing to be bound to any theory regarding mode of action, it is believed that the compounds of the present invention are potassium ion channel "blockers", more specifically charybdotoxin-sensitive-potassium-channel "blockers", and ATP-dependent-potassium-channel "blockers".

The term "cardiac ischaemia" (also known as "ischaemic heart disease") as used herein denotes a clinical condition wherein there is an inadequate supply of blood to the heart (so that oxygen demand from the heart exceeds supply). The term includes conditions such as angina pectoris, myocardial infarction, arrhythmias and many forms of heart failure.

The term "cerebral ischaemia" as used herein denotes a clinical condition wherein there is an inadequate supply of blood to the central nervous system, especially the brain. The term includes conditions such as stroke, brain trauma, head injuries and haemorrhage.

The term "convulsion" as used herein denotes a clinical condition giving rise to seizures and/or convulsions. It includes neurological disorders such as epilepsy.

Compounds of formula I may exist as salts with pharmaceutically acceptable acids. Examples of such salts include hydrochlorides, hydrobromides, sulphates, methanesulphonates, nitrates, maleates, acetates, citrates, fumarates, tartrates [eg (+)-tartrates, (-)-tartrates or mixtures thereof including racemic mixtures], succinates, benzoates and salts with amino acids such as glutamic acid. Compounds of formula I and their salts may exist in the form of solvates (for example hydrates).

It will be appreciated by those skilled in the art that compounds of formula I may contain a chiral centre. When a compound of formula I contains a single chiral centre it may exist in two enantiomeric forms. The present invention includes the use of the individual enantiomers and mixtures of the enantiomers. The enantiomers may be resolved by methods known to those skilled in the art, for example by formation of diastereoisomeric salts or complexes which may be separated, for example, by crystallisation; via formation of diastereoisomeric derivatives which may be separated, for example, by crystallisation, gas-liquid or liquid chromatography; selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic oxidation or reduction, followed by separation of the modified and unmodified enantiomers; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support, for example silica with a bound chiral ligand or in the presence of a chiral solvent. It will be appreciated that where the desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step is required to liberate the desired enantiomeric form. Alternatively, specific enantiomers may be synthesised by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer to the other by asymmetric transformation.

When a compound of formula I contains more than one chiral centre it may exist in diastereoisomeric forms. The diastereoisomeric pairs may be separated by methods known to those skilled in the art, for example chromatography or crystallisation and the individual enantiomers within each pair may be separated as described above. The present invention included each diastereoisomer of compounds of formula I and mixtures thereof.

Certain compounds of formula I and their salts may exist in more than one crystal form and the present invention includes each crystal form and mixtures thereof. Certain compounds of formula I and their salts may also exist in the form of solvates, for example hydrates, and the present invention includes each solvate and mixtures thereof.

The compound of formula I may be administered in any of the known pharmaceutical dosage forms. The amount of the compound to be administered will depend on a number of factors including the age of the patient, the severity of the condition and the past medical history of the patient and always lies within the sound discretion of the administering physician but it is generally envisaged that the dosage of the compound to be administered will be in the range 150 to 1500 mg preferably 250 to 500 mg per day given in one or more doses.

Oral dosage forms are the preferred compositions for use in the present invention and these are the known pharmaceutical forms for such administration, for example tablets, capsules, granules, syrups and aqueous or oil suspensions. The excipients used in the preparation of these compositions are the excipients known in the pharmacist's art. Tablets may be prepared from a mixture of the active compound with fillers, for example calcium phosphate; disintegrating agents, for example maize starch; lubricating agents, for example magnesium stearate; binders, for example microcrystalline cellulose or polyvinylpyrrolidone and other optional ingredients known in the art to permit tableting the mixture by known methods. The tablets may, if desired, be coated using known methods and excipients which may include enteric coating using for example hydroxypropylmethylcellulose phthalate. The tablets may be formulated in a manner known to those skilled in the art so as to give a sustained release of the compounds of the present invention. Such tablets may, if desired, be provided with enteric coatings by known methods, for example by the use of cellulose acetate phthalate. Similarly, capsules, for example hard or soft gelatin capsules, containing the active compound with or without added excipients, may be prepared by known methods and, if desired, provided with enteric coatings in a known manner. The contents of the capsule may be formulated using known methods so as to give sustained release of the active compound. The tablets and capsules may conveniently each contain 1 to 500 mg of the active compound.

Other dosage forms for oral administration include, for example, aqueous suspensions containing the active compound in an aqueous medium in the presence of a non-toxic suspending agent such as sodium carboxymethylcellulose, and oily suspensions containing a compound of the present invention in a suitable vegetable oil, for example arachis oil. The active compound may be formulated into granules with or without additional excipients. The granules may be ingested directly by the patient or they may be added to a suitable liquid carrier (for example, water) before ingestion. The granules may contain disintegrants, eg an effervescent couple formed from an acid and a carbonate or bicarbonate salt to facilitate dispersion in the liquid medium.

The therapeutically active compounds of formula I may be formulated into a composition which the patient retains in his mouth so that the active compound is administered through the mucosa of the mouth.

Dosage forms suitable for rectal administration are the known pharmaceutical forms for such administration, for example, suppositories with cocoa butter or polyethylene glycol bases.

Dosage forms suitable for parenteral administration are the known pharmaceutical forms for such administration, for example sterile suspensions or sterile solutions in a suitable solvent.

Dosage forms for topical administration may comprise a matrix in which the pharmacologically active compounds of the present invention are dispersed so that the compounds are held in contact with the skin in order to administer the compounds transdermally. A suitable transdermal composition may be prepared by mixing the pharmaceutically active compound with a topical vehicle, such as a mineral oil, petrolatum and/or a wax, e.g. paraffin wax or beeswax, together with a potential transdermal accelerant such as dimethyl sulphoxide or propylene glycol. Alternatively the active compounds may be dispersed in a pharmaceutically acceptable cream, gel or ointment base. The amount of active compound contained in a topical formulation should be such that a therapeutically effective amount of the compound is delivered during the period of time for which the topical formulation is intended to be on the skin.

The therapeutically active compound of formula I may be formulated into a composition which is dispersed as an aerosol into the patients oral or nasal cavity. Such aerosols may be administered from a pump pack or from a pressurised pack containing a volatile propellant.

The therapeutically active compounds of formula I used in the method of the present invention may also be administered by continuous infusion either from an external source, for example by intravenous infusion or from a source of the compound placed within the body. Internal sources include implanted reservoirs containing the compound to be infused which is continuously released for example by osmosis and implants which may be (a) liquid such as an oily suspension of the compound to be infused for example in the form of a very sparingly water-soluble derivative such as a dodecanoate salt or a lipophilic ester or (b) solid in the form of an implanted support, for example of a synthetic resin or waxy material, for the compound to be infused. The support may be a single body containing all the compound or a series of several bodies each containing part of the compound to be delivered. The amount of active compound present in an internal source should be such that a therapeutically effective amount of the compound is delivered over a long period of time.

In some formulations it may be beneficial to use the compounds of the present invention in the form of particles of very small size, for example as obtained by fluid energy milling.

In the compositions of the present invention the active compound may, if desired, be associated with other compatible pharmacologically active ingredients.

The biological action of the compounds used in the present invention will be better understood with reference to the following example.

Example

Hearts from male Olac Wistar strain rats (250-300g) were perfused via the aorta with Krebs Henseleit Bicarbonate buffer (using a procedure adapted from Neely & Rovetto, "Techniques for perfusing isolated rat hearts", Methods in Enzymology 1975; 38:43-60). Left ventricular pressure and heart rate were continuously monitored. Following a 15-20 minute stabilisation period, hearts were perfused for a further 10 minute period either with test compound or buffer. The heart was then made globally ischaemic by abolishing the flow of perfusate for 45 minutes. The heart was then reperfused for 30 minutes. The haemodynamic function of the heart was monitored by measuring heart rate (HR) and left ventricular developed pressure (LVDP) (based on Grover et al in The Journal of Pharmacology and Experimental Therapeutics, 1989; 98-104). The following two parameters were used to assess the antiischaemic activity of compounds.

(i) The % recovery of haemodynamic function was assessed by calculating the ‘double product’ (DP) (HR x LVDP) measured prior to the onset of ischaemia and at the end of the 30 minute reperfusion period. This was subject to statistical analysis using the Mann-Whitney test.

(ii) The number of hearts demonstrating any signs of recovery were determined and expressed as a fraction of the total group size eg. 2/6, 3/4. Data was analysed using Fisher's exact test.

A compound was considered to be active in this test if it significantly improved both the % recovery of double product and the number of hearts recovering within the group ($p<0.05$) compared to controls with vehicle only.

Results for the control (A) and for selected compounds (B to Q) within the scope of Formula I are set out below in Table 1.

In the table, "sig" denotes statistical significance with respect to the preceding column, with "ns" denoting "no significance", "*" denoting significance at the 5% level, "**" denoting significance at the 1% level and "***" denoting significance at the 0.1% level.

"Recovery No." denotes the number of hearts recovering (shown over the total number of hearts in the group). "DP" is defined above.

Table 1

	Compound	Dosage Conc. (µM)	% DP	Sig	Recovery No.	Sig
A	Control	-	11.8	-	44/235	-
B	1,1-dimethyl-2-(2-morpholinophenyl)-guanidine monofumarate	100.0 30.0 10.0	40.650 16.100 0.000	* ns ns	5/8 3/8 0/8	** ns ns
C	1-(n-butyl)-2-(2-morpholinophenyl)-3-methylguanidine monofumarate	30.0 10.0	46.000 0.000	* ns	3/4 0/4	* ns
D	N,N-dimethyl-N′-(2-morpholinophenyl)-propionamidine	100.0 30.0	30.530 19.800	* *	3/6 2/7	* *
E	1,1-dimethyl-2-(3-methyl-2-morpholinophenyl)guanidine monofumarate	100.0 100.0 30.0	44.500 30.260 0.000	* * ns	2/2 2/4 0/4	* ns ns
F	1-(n-butyl)-2-(5-methyl-2-morpholino-phenyl)-3-methylguanidine monofumarate	10.0	68.000	*	4/4	**

	Compound	Dosage Conc. (μM)	% DP	Sig	Recovery No.	Sig
G	1-(n-butyl)-2-(6-methyl-2-morpholinophenyl)-3-methylguanidine monofumarate	100.0	46.750	*	6/6	***
		30.0	58.700	*	3/4	**
		10.0	34.400	*	5/10	**
		3.0	28.600	*	3/6	*
		1.0	38.700	*	4/8	*
		0.3	20.250	ns	2/6	ns
H	N-butyl-N'-(2-fluoro-6-morpholinophenyl)-N''-methylguanidine monofumarate	10.0	53.500	*	3/4	*
I	N-butyl-N'-(2,6-dimorpholinophenyl)-N''-methylguanidine monofumarate	10.0	68.500	*	3/3	**
J	N-butyl-N'-methyl-N''-[2-methyl-6-(perhydro-4H-1,4-thiazin-4-yl)phenyl]-guanidine monofumarate	10.0	68.500	*	4/4	***
K	N-butyl-N'-methyl-N''-(2-methyl-6-piperidinophenyl)guanidine	10.0	70.300	*	3/3	**

	Compound	Dosage Conc. (µM)	% DP	Sig	Recovery No.	Sig
L	N-butyl-N′-methyl-N′′-(2-methyl-6-morpholinomethylphenyl)guanidine monofumarate	30.0	54.400	*	4/4	***
		10.0	78.700	*	4/4	***
		3.0	14.800	ns	1/4	ns
M	N-butyl-N′-methyl-N′′-(3-methylbiphenyl-2-yl)guanidine monofumarate	10.0	64.300	*	4/4	***
		3.0	42.300	*	3/4	*
		1.0	67.600	*	6/7	***
		0.3	42.500	*	4/7	*
N	N-butyl-N′-methyl-N′′-(2-tolyl)guanidine monofumarate	30.0	51.400	*	3/4	*
		10.0	59.800	*	3/4	*
		3.0	0.000	ns	0/4	ns
O	N-methyl-N′-(6-methyl-2-morpholinophenyl)-N′′-pentylguanidine monofumarate	30.0	59.550	*	4/4	**
		10.0	70.200	*	3/4	*
		3.0	34.800	*	4/8	*
		1.0	17.600	ns	1/3	ns

	Compound	Dosage Conc. (μM)	% DP	Sig	Recovery No.	Sig
P	N-butyl-N,N''-dimethyl-N'-(6-methyl-2-morpholinophenyl)guanidine monofumarate	30.0	71.200	*	4/4	***
		10.0	76.750	*	4/4	***
		3.0	41.300	*	4/8	*
		1.0	38.100	*	4/7	*
Q	N-butyl-N',N'-dimethyl-N''-(2-methyl-6-morpholinophenyl)guanidine	10.0	47.000	*	3/4	*

The following compounds within the scope of formula I above are believed to be new _per se_:

_N_-butyl-_N_′-(2-fluoro-6-morpholinophenyl)-_N_′′-methylguanidine;
_N_-butyl-_N_′-(2,6-dimorpholinophenyl)-_N_′′-methylguanidine;

_N_-butyl-_N_′-methyl-_N_′′-[2-methyl-6-(perhydro-4_H_-1,4-thiazin-4-yl)phenyl]guanidine;
_N_-butyl-_N_′-methyl-_N_′′-(2-methyl-6-piperidinophenyl)guanidine;
_N_-butyl-_N_′-methyl-_N_′′-(2-methyl-6-morpholinomethylphenyl)guanidine;
_N_-butyl-_N_′-methyl-_N_′′-(3-methylbiphenyl-2-yl)guanidine;
_N_-butyl-_N_′-methyl-_N_′′-(2-tolyl)guanidine;
_N_-methyl-_N_′-[6-methyl-2-morpholinophenyl]-_N_′′-pentylguanidine;
_N_-butyl-_N_,_N_′′-dimethyl-_N_′-[6-methyl-2-morpholinophenyl]guanidine;
_N_-butyl-_N_′,_N_′-dimethyl-_N_′′-(2-methyl-6-morpholinophenyl)guanidine;

and pharmaceutically acceptable salts thereof, and are claimed as a further aspect of the present invention.

The invention is further illustrated by the following non-limitative Examples in which compositions of mixed solvents are given by volume. Novel compounds were characterised by one or more of the following: elemental analysis, nuclear magnetic resonance and infra-red spectroscopy.

Flash chromatography was performed according to the method of Still _et al_, J. Org. Chem. (1978), Vol. 43, pp 2923-5.

All hydrogenations with palladium/charcoal were carried out at atmospheric pressure and ambient temperature.

Example 1

a) A solution of 2,6-difluoronitrobenzene (19.5g; preparable as described in J. Med. Chem. (1968) 11, 814) and morpholine (23.5 ml) in dry toluene (100 ml) was stirred and heated on a steam bath (95-100°C) for 2 hours. The mixture was evaporated and the residue was purified by flash column chromatography on silica gel eluting with dichloromethane to give 4-(3-fluoro-2-nitrophenyl)morpholine (20.81 g).

b) A solution of 4-(3-fluoro-2-nitrophenyl)morpholine (10 g; see 1 (a) above) in dry ethanol (200 ml) was hydrogenated over 10% palladium on charcoal (0.5 g). The mixture was filtered through diatomaceous earth (available under the trade name "Celite"), the filter pad was washed with industrial methylated spirits (2 x 100 ml) and the filtrate was evaporated. The residue was dissolved in dichloromethane (200 ml), dried over magnesium sulphate and then evaporated to give 2-fluoro-6-morpholinoaniline as an oil (8.81 g).

c) A solution of 2-fluoro-6-morpholinoaniline (8.8 g; see 1 (b) above) and methyl isothiocyanate (5 ml) in dichloromethane (150 ml) was left at ambient temperature for 3 days. The resulting solution was evaporated and the residue was triturated with diethyl ether (200 ml) to give N-(2-fluoro-6-

morpholinophenyl)-N'-methylthiourea (6.91 g) as a violet solid.

d) A solution of N-(2-fluoro-6-morpholinophenyl)-N'-methylthiourea (6.9 g; see 1 (c) above) and methyl iodide (1.8 ml) in dry acetone (70 ml) was boiled under reflux for 2 hours. Further methyl iodide (1.8 ml) was added and boiling was continued for 1 hour. The solution was then evaporated and the residue was dissolved in ethanol (100 ml). Butylamine (2.5 ml), potassium hydroxide (1.5 g) and lead (II) acetate trihydrate (3.24 g) were added and the resulting mixture was boiled under reflux for approximately 16 hours. The resulting mixture was evaporated and the residue was treated with water (200 ml) and dichloromethane (200 ml) and then filtered through diatomaceous earth (available under the trade name "Celite"). The filter pad was washed with water (2 x 100 ml) and dichloromethane (2 x 100 ml). The dichloromethane layer was extracted with dilute hydrochloric acid (3 x 200 ml) and the acidic extracts were basified with concentrated (15 M) aqueous sodium hydroxide solution to pH 10. The basified extracts were extracted with dichloromethane (4 x 200 ml) and the organic phases were dried over magnesium sulphate and then evaporated. The residue was dissolved in ethanol (30 ml) and fumaric acid (1.88 g) was added. The resulting solution was stirred and boiled under reflux for 1 hour and then added dropwise into stirred diethyl ether (1 l) to give a grey precipitate (hygroscopic). The precipitate was dried in vacuo at 40°C over phosphorus pentoxide to give N-butyl-N'-(2-fluoro-6-morpholinophenyl)-N''-methylguanidine monofumarate (5.41 g, m.pt. 80-85°C).

Example 2

a) 2,6-Difluoronitrobenzene (20 g; preparable as described in J. Med. Chem. (1968) 11, 814) and morpholine (100 ml), were stirred under reflux for 3½ hours. The excess morpholine was distilled off at reduced pressure and the resulting residue was extracted with diethyl ether (2 x 300 ml). The extracts were then evaporated to give an orange solid. Further extraction of this residue with diethyl ether (6 x 300 ml) gave 2,6-dimorpholinonitrobenzene (13.66 g; m.pt 175-178°C).

b) A solution of 2,6-dimorpholinonitrobenzene (23.00 g; see 2 (a) above) in ethanol (300 ml) was hydrogenated over 10% palladium on charcoal (2 g). The resulting mixture was filtered through diatomaceous earth (available under the trade name ("Celite"), the filter pad was washed with industrial methylated spirits (2 x 100 ml) and the filtrate was evaporated. The resulting residue was dissolved in dichloromethane (200 ml), dried over magnesium sulphate and then evaporated to give 2,6-dimorpholinoaniline (16.02 g; m.pt. 105-107°C).

c) 2,6-Dimorpholinoaniline (16.00 g; see 2 (b) above) and methyl isothiocynate (6.7 g) were dissolved in dichloromethane (200 ml) and left at ambient temperature for 24 hours. The resulting solution was stirred and boiled under reflux for approximately 3 days and then evaporated. The residue was triturated with diethyl ether (100 ml) to give N-methyl-N'-(2,6-dimorpholinophenyl)-thiourea (14.43 g) as a pale brown solid.

d) A solution of methyl iodide (1.6 ml, 26.2 mmols) and N-methyl-N′-(2,6-dimorpholinophenyl)thiourea (8 g; see 2 (c) above) in dry acetone (100 ml) was boiled under reflux for 2 hours. The resulting solution was evaporated to give a brown gum which was dissolved in ethanol (100 ml). Butylamine (2.4 ml), lead (II) acetate trihydrate (9.00 g) and potassium hydroxide (1.33 g) were added and the resultant mixture was boiled under reflux for approximately 16 hours. The resulting mixture was evaporated and the resulting residue was treated with water (150 ml) and dichloromethane (150 ml). The resulting suspension was filtered through diatomaceous earth (available under the trade name "Celite") and the filter pad was washed with water (2 x 100 ml) and dichloromethane (2 x 100 ml). The filtrate layers were separated and the organic layer was extracted with 2M hydrochloric acid (3 x 100 ml). The acidic extracts were combined with the previous aqueous phase and basified to pH 10 with 5M sodium hydroxide solution. The aqueous phase was extracted with dichloromethane (4 x 100 ml) and the organic extracts were dried over magnesium sulphate and then evaporated. The resulting residue was heated under reflux in a mixture of ethanol (30 ml) and fumaric acid (2.21 g) for 1 hour. The resulting solution was cooled to ambient temperature and was added dropwise over 1 hour to stirred, dry diethyl ether (1.2 l) to give a grey precipitate (very hygroscopic) which was dried in vacuo at 40°C over phosphorus pentoxide. The solid was dissolved in dry ethanol (25 ml). Fumaric acid (0.22 g) was added and the resulting solution was heated under reflux for 1 hour. The resulting solution was cooled to ambient temperature and was added dropwise over one hour to stirred, dry diethyl ether (1.2 l) to give a grey precipitate which was dried <u>in vacuo</u> at 40°C over phosphorus pentoxide. This solid was dissolved in water (100 ml), basified to pH 11 with 5M sodium hydroxide solution and extracted with dichloromethane (4 x 150 ml). The organic phases were dried over magnesium sulphate and evaporated to give a brown oil which was purified by flash column chromatography on silica gel eluting with industrial methylated spirits/triethylamine (9:1). The purified oil (6.2 g) was dissolved in ethanol (20 ml). Fumaric acid (1.92 g) was added and the resulting solution was boiled under reflux for 1½ hours. The solution was cooled to ambient temperature and added dropwise to stirred, dry diethyl ether (1 l). The resulting precipitate was collected and dried <u>in vacuo</u> at 40°C to give <u>N</u>-butyl-<u>N</u>′-(2,6-dimorpholinophenyl)-<u>N</u>′′-methylguanidine monofumarate (4.14 g; m.pt. approximately 90°C).

<u>Example 3</u>

a) A mixture of thiomorpholine (34.4 g) and 3-chloro-2-nitrotoluene (19.1 g) was boiled under reflux for 5 hours (175°C). The mixture was left to cool for approximately 16 hours and the product was extracted into diethyl ether (3 x 500 ml). The diethyl ether was distilled off to give a black oil. This oil was purified by flash chromatography on silica gel eluting with petroleum ether (bp 60-80°C)/dichloromethane (5:1) and the product fractions were evaporated to give 2-nitro-3-(perhydro-4<u>H</u>-1,4-thiazin-4-yl)toluene (17.8 g, m. pt. 79-85°C) as a yellow solid.

b) A solution of 2-nitro-3-(perhydro-4H-1,4-thiazin-4-yl)toluene (17.8 g; see 3 (a) above) in dry toluene (150 ml) was placed in a hydrogenation vessel and palladium on charcoal (10%, 1.75 g) in dry toluene (50 ml) was added. The resulting suspension was hydrogenated and then left for approximately 16 hours. Absolute ethanol (50 ml) was added to the resulting mixture followed by a slurry of palladium on charcoal (10%, 1.5 g) in dry toluene (30 ml) and the resulting mixture was hydrogenated once again for 7½ hours. The mixture was then filtered through diatomaceous earch (available under the trade name "Celite") and the residue was washed with ethanol (150 ml). The ethanol was distilled off and the residue was dissolved in petroleum ether (60-80°C, 300 ml). Charcoal was added and the resulting mixture was boiled under reflux for 10 minutes. The mixture was filtered hot, evaporated to 200 ml and cooled to 0°C. The resultant solid was filtered off, washed with petroleum ether (bp 60-80°C, 100 ml) and dried in vacuo at 40°C to give 2-methyl-6-(perhydro-4H-1,4-thiazin-4-yl)aniline (11.17 g; m.pt. 84-85°C).

c) A solution of 2-methyl-6-(perhydro-4H-1,4-thiazin-4-yl)aniline (11.17 g; see 3 (b) above) and methyl isothiocyanate (6 ml) in dichloromethane (70 ml) was stirred at ambient temperature for 24 hours. The solvent was distilled off and the residue was ground under petroleum ether (bp 60-80°C, 100 ml), and filtered to give a white solid which was dried in vacuo to give N-methyl-N′-[2-methyl-6-(perhydro-4H-1,4-thiazin-4-yl)phenyl]thiourea (14.7g; m.pt. 153-156°C).

d) A mixture of _N_-methyl-_N_'-[2-methyl-6-(perhydro-4_H_-1,4-thiazin-4-yl)phenyl]thiourea (14.7 g; see 3 (c) above), methyl iodide (7.4 g, 3.6 ml) and dry acetone (140 ml) was stirred and boiled under reflux for 4 hours. The acetone was distilled off and the resulting residue was washed with petroleum ether (bp 60-80°C, 100 ml) and dried _in vacuo_ at 60°C to give 2-methyl-1-[2-methyl-6-(perhydro-4_H_-1,4-thiazin-4-yl)phenyl]-3-methyl-2-thiopseudourea hydroiodide (21.74 g; m.pt. 186-191°C).

e) A suspension of 2-methyl-1-[2-methyl-6-(perhydro-4_H_-,4-thiazin-4-yl)phenyl]-3-methyl-2-thiopseudourea hydroiodide (21.74 g; see 3 (d) above), potassium hydroxide (2.7 g), butylamine (7.7 g) and lead (II) acetate trihydrate (8.9 g) in absolute ethanol was boiled under reflux for 21 hours. More butylamine (5.2 ml), potassium hydroxide (1.4 g), ethanol (35 ml) and lead (II) acetate trihydrate (4.5 g) were added and the resulting mixture was boiled under reflux for a further 6 hours. The ethanol was then distilled off and water (100 ml) and dichloromethane (100 ml) were added to the resulting residue. The resulting mixture was stirred for 15 minutes at ambient temperature and then left for approximately 16 hours. The mixture was then filtered through diatomaceous earth (available under the trade name "Celite") and the residue was washed with dichloromethane (4 x 100 ml). The dichloromethane phase was separated off and the aqueous phase was washed with dichloromethane (1 x 100 ml). All dichloromethane phases were combined and extracted into 3M hydrochloric acid (3 x 100 ml) and the acidic aqueous phases were backwashed with dichloromethane (1 x 100 ml). The acidic aqueous phase was then basified with 5M aqueous sodium hydroxide solution and the basic mixture was extracted with dichloromethane (3 x 100 ml). The extracts were dried over magnesium sulphate and then filtered and evaporated to give a light brown oil (17 g). 7.8 g of this oil was refluxed with ethanol (2.5 ml) and fumaric acid (2.8 g) for 1½ hours. The resulting mixture was added to diethyl ether (200 ml) and the resultant gummy solid was washed with diethyl ether (4 x 100 ml) to give a solid which was filtered off and dried in vacuo at 60°C to give N-butyl-N′-methyl-N′′-[2-methyl-6-(perhydro-4H-1,4-thiazin-4-yl)phenyl]guanidine monofumarate (7 g; m.pt. 168-170°C) as a white solid.

Example 4

a) 3-Chloro-2-nitrotoluene (15 g) was heated with piperidine (74.3 g) at approximately 95°C for 96 hours and the resulting mixture was distilled under reduced pressure to dryness. The product was purified by flash chromatography on silica gel eluting with petroleum ether (bp 40-60°C)/ dichloromethane (5:1) to provide N-(3-methyl-2-nitrophenyl)piperidine (18.75 g; m.pt. 45°C).

b) N-(3-Methyl-2-nitrophenyl)piperidine (18.66g; see 4 (a) above) was hydrogenated over 10% palladium on carbon (600 mg) in toluene (100 ml) and industrial methylated spirits (200 ml). The resulting mixture was filtered through diatomaceous earth (available under the trade name "Celite") then the solution was hydrogenated over platinum oxide (300 mg). The resulting mixture was then hydrogenated in a sealed pressure vessel at 50°C (5 bar) for approximately 16 hours, filtered through diatomaceous earth (available under the trade name "Celite") and evaporated to dryness. The mixture was purified by flash chromatography on silica gel, eluting with dichloromethane/petroleum ether (bp 40-60°C (2:1) to provide N-(2-amino-3-methylphenyl)piperidine (13.11 g; m.pt 52-55°C).

c) N-(2-Amino-3-methylphenyl)piperidine (12.93 g; see 4 (b) above) and methyl isothiocyanate (7.45 g) were left together in dry dichloromethane (150 ml) at ambient temperature for approximately 70 hours and then boiled under reflux for approximately 7 hours. The resulting solution was distilled to dryness and purified by flash chromatography on silica gel eluting with dichloromethane to provide N-methyl-N′-(2-methyl-6-piperidinophenyl)thiourea (13.09 g; m.pt. 125-129°).

d) N-Methyl-N′-(2-methyl-6-piperidinophenyl)thiourea (13.06 g; see 4 (c) above) and methyl iodide (3.4 ml) in acetone (130 ml) was boiled under reflux for approximately 2¾ hours. The resulting mixture was distilled to dryness and crystallised from petroleum ether (bp 40-60°, 500 ml) to provide 2-methyl-3-methyl-1-(2-methyl-6-piperidinophenyl)pseudothiourea hydroiodide (18.73 g; m.pt. 165-169°C).

e) Potassium hydroxide (2.3 g), butylamine (9.09 ml), lead (II) acetate trihydrate (7.9 g) and 2-methyl-3-methyl-1-(2-methyl-6-piperidinophenyl)pseudothiourea hydroiodide (18.65 g; see 4 (d) above) were stirred together in absolute ethanol (70 ml) with boiling under reflux for approximately 100 hours. The ethanol was distilled off and the resulting residue was dissolved in a mixture of water (100 ml) and dichloromethane (100 ml). The resulting mixture was filtered together through diatomaceous earth (available under the trade name "Celite"). The aqueous phase was separated and the dichloromethane layer was washed with 3M hydrochloric acid (2 x 100 ml). The acid phase was washed with dichloromethane (100 ml) and then basified with 5M aqueous sodium hydroxide solution. The basic phase was extracted with dichloromethane (3 x 150 ml) and the combined basic extracts were dried over magnesium sulphate and then distilled to dryness to give an oil. This oil was dissolved in a minimum of absolute ethanol (approximately 100 ml) and combined with fumaric acid (5.18 g) also in a minimum of absolute ethanol (200 ml). The resulting mixture was boiled under reflux for 1½ hours and then cooled to ambient temperature. The mixture was added to diethyl ether (1l) to give an oil which was crystallized from industrial methylated spirits (100 ml) to give N-butyl-N'-methyl-N''-(2-methyl-6-piperidinophenyl)guanidine (16.05 g; m.pt. 73-75°C).

Example 5

a) A solution of 3-methyl-2-nitrobenzyl bromide (16 g; preparable as described in Tetrahedron Letters (1982) 23, 1829) in toluene (100 ml) was added over 10 minutes to morpholine (250 ml) on a steam bath at 95-100°C and the resulting mixture was then heated at 95-100° for 10 minutes. The solvents were removed by distillation under reduced pressure and water (200 ml) was added to the residue. The resulting mixture was basified with sodium hydroxide solution (5M, 50 ml) and then extracted with ethyl acetate (2 x 200 ml). The combined organic layers were extracted with hydrochloric acid (5M, 200 ml) and the acidic extract was basified with sodium hydroxide solution (15M) with ice cooling. The aqueous mixture was extracted with ethyl acetate (2 x 100 ml) and the combined extracts were washed with water (100 ml), dried over magnesium sulphate and evaporated to give 4-(3-methyl-2-nitrobenzyl)morpholine (11 g; m.pt. 35°C) as an oil which solidified after 5 days.

b) A mixture of 4-(3-methyl-2-nitrobenzyl)morpholine (1.03 g; see 5 (a) above), palladium on charcoal (10%, 0.2 g) and ethanol (100 ml) was hydrogenated at atmospheric pressure for 40 minutes and then filtered through diatomaceous earth (available under the trade name "Celite"), washing the filter bed with ethanol (2 x 50 ml). The combined filtrates were evaporated to dryness and the resulting residue was extracted with diethyl ether (200 ml). The extract was dried over magnesium sulphate and evaporated to dryness to provide 4-(2-amino-3-methylbenzyl)morpholine (0.8 g) as an oil.

c) A solution of 4-(2-amino-3-methylbenzyl)morpholine (8.8 g; see 5 (b) above) and methyl isothiocyanate (6 g) in dichloromethane (60 ml) was left for approximately 3 days at ambient temperature and then evaporated under reduced pressure to dryness. The residue was triturated with diethyl ether (15 ml) to give <u>N</u>-methyl-<u>N</u>′-(2-methyl-6-morpholinomethylphenyl)thiourea (11.1 g; m.pt. 105-107°C) as a white solid.

d) Methyl iodide (0.22 ml) was added to a solution of N-methyl-N'-(2-methyl-6-morpholinomethylphenyl)-thiourea (1 g; see 5 (c) above) in methanol (30 ml) and the solution was left for approximately 16 hours at ambient temperature. Further methyl iodide (0.1 ml) was added and the resulting mixture was left for a further 24 hours (approx). The solvent was removed by distillation to give the hydroiodide salt (1.5 g), which was dissolved in ethanol (20 ml). Butylamine (0.73 ml), potassium hydroxide (0.18 g) and lead (II) acetate trihydrate (0.64 g) were added and the resulting mixture was stirred and boiled under reflux for approximately 16 hours. The solvent was removed by distillation and water (50 ml) followed by dichloromethane (100 ml) were added to the residue. The resulting mixture was stirred for 10 minutes, and filtered through diatomaceous earth (available under the trade name "Celite"), washing the filter pad with dichloromethane (2 x 50 ml). The layers were separated and the dichloromethane layer was washed with water (50 ml) before being extracted with hydrochloric acid (1M, 100 ml). The acidic extract was washed with dichloromethane (30 ml), basified with aqueous sodium hydroxide solution (5M) and then extracted with dichloromethane (4 x 50 ml). The combined extracts were dried over magnesium sulphate and evaporated to give an oil (0.9 g). The reaction was repeated on a 4.9 x scale. The combined products were dissolved in methanol (30 ml), fumaric acid (1.9 g) was added and the resulting mixture was heated under reflux for approximately 1 hour. The resulting solution was poured into diethyl ether (1½ l) and stirred vigorously. The initially gummy substance slowly solidified and was subsequently triturated with diethyl ether (500 ml), collected and dried to give N-butyl-N′-methyl-N′′-(2-methyl-6-morpholinomethylphenyl)guanidine monofumarate (3.55 g; m.pt. 114-117°C).

Example 6

a) A mixture of 2-amino-3-methylbiphenyl (7.2 g; preparable as described in WO 92/00273 in the name of The Boots Company PLC), methyl isothiocyanate (4.3 g) and dichloromethane (100 ml) was left at ambient temperature for approximately 6 hours and then boiled under reflux for 2 days. Further methyl isothiocyanate (2.2 g) in dichloromethane (20 ml) was added and the reflux was continued for a further day. The solvent was removed by distillation and replaced by toluene (40 ml) and then further methyl isothiocyanate (2 g) was added. The resulting mixture was heated at 100°C for a further day and then evaporated to dryness. The resulting residue was crystallised from toluene (80 ml) to give N-methyl-N′-(3-methylbiphenyl-2-yl)thiourea (7 g; m.pt. 165-168°C).

b) A mixture of N-methyl-N′-(3-methylbiphenyl-2-yl)thiourea (6.7 g; see 6 (a) above), methyl iodide (1.9 ml) and dry acetone (100 ml) was heated under reflux for 2 hours and the solvent was removed by distillation. Butylamine (5.1 ml), potassium hydroxide (1.26 g), lead (II) acetate trihydrate (4.48 g) and ethanol (150 ml) were then added and the resulting mixture was stirred under reflux for approximately 16 hours. The solvent was removed by distillation and the resulting residue was extracted with a mixture of water (200 ml) and dichloromethane (200 ml). The phases were separated and the dichloromethane layer was evaporated to dryness. The resulting residue was purified by flash chromatography on silica gel eluting with ethyl acetate/triethylamine/ methanol (10:1:1) to give the free base of the product, (4.6 g). This was dissolved in ethanol (30 ml). Fumaric acid (1.81 g) was added and the resulting mixture was boiled under reflux for approximately 30 minutes. The resulting solution was then added slowly to diethyl ether (1 l) with stirring. The resulting precipitate was collected by filtration and washed with diethyl ether (2 x 100 ml) and then dried to give N-butyl-N′-methyl-N′′-(3-methylbiphenyl-2-yl)guanidine monofumarate (5.25 g; m.pt. 116-120°C).

Example 7

a) A solution of o-toluidine (24.5 ml; available from the Aldrich Chemical Company, UK) and methyl isothiocyanate (24 ml) in dichloromethane (300 ml) was stirred at ambient temperature for 18 hours. The solvent was distilled off and the resulting residue was washed with petroleum ether (bp 60-80°C; 2 x 200 ml) and filtered to give a purple solid. This solid was ground up and washed with industrial methylated spirits (2 x 100 ml) to give a white solid which was dried *in vacuo* at 60°C to give N-methyl-N′-(2-tolyl)thiourea (35.38 g; m.pt. 157-160°C).

b) A mixture of N-methyl-N′-(2-tolyl)thiourea (35.38 g; see 7 (a) above), methyl iodide (30.7 g) and dry acetone (450 ml) was stirred at reflux for 4½ hours. The acetone was distilled off and the resulting residue was washed with petroleum ether (bp 60-80°C; 2 x 250 ml) to give a white solid which was dried in vacuo at 60°C to give 2-methyl-1-(2-tolyl)-3-methyl-2-thiopseudourea hydroiodide (61.95 g; m.pt. 174-176°C).

c) A mixture of 2-methyl-1-(2-tolyl)-3-methyl-2-thiopseudourea hydroiodide (20 g; see 7 (b) above), butylamine (9.3 g), absolute ethanol (86 ml), potassium hydroxide (3.2 g) and lead (II) acetate trihydrate (10.7 g) was refluxed for approximately 18 hours. More butylamine (6.3 ml), ethanol (43 ml), potassium hydroxide (1.6 g) and lead (II) acetate trihydrate (5.4 g) were added and the resulting suspension was stirred at reflux for a further 5 hours. The ethanol was distilled off and water (100 ml) and dichloromethane (100 ml) were added. The resulting mixture was stirred for 15 minutes at ambient temperature and filtered through diatomaceous earth (available under the trade name "Celite"). The filter pad was washed with more dichloromethane (3 x 100 ml). The dichloromethane phase was separated off and extracted with 3M hydrochloric acid (3 x 100 ml). The acidic extracts were backwashed with dichloromethane (1 x 100 ml), basified to pH 14 with aqueous sodium hydroxide solution (15 M), extracted with dichloromethane (3 x 150 ml) and the extracts were then dried over magnesium sulphate, filtered and evaporated to give a clear oil (8.5 g). The fumarate salt was prepared by refluxing the oil (8.5 g) with fumaric acid (4.5 g) in ethanol (40 ml) for 1¼ hours then adding diethyl ether (100 ml) and cooling to 0°C. The resulting solid was filtered off, washed with more diethyl ether (1 x

50 ml) and dried in vacuo at 60°C to give N-butyl-N'-methyl-N''-(2-tolyl)guanidine monofumarate (5.4 g; m.pt. 120-125°C).

Example 8

a) A solution of 3-chloro-2-nitrotoluene (17 g; preparable as described in Cohen and Hodsham, JCS (1907) 91, 974) and morpholine (27 ml) in dry toluene (100 ml) was stirred and refluxed for 24 hours. The toluene was distilled off, more morpholine (50 ml) was added and the resulting solution was refluxed for 24 hours. More 3-chloro-2-nitrotoluene (94.1 g) and more morpholine (350 ml) were added to the solution and the resulting solution was stirred at reflux for approximately 3 days. Excess morpholine was then distilled off and the residue was washed with ether (3 x 500 ml) and ethyl acetate (2 x 800 ml) to extract the product. The ether and ethyl acetate phases were combined and concentrated to give a brown solid. This solid was purified by flash column chromatography on silica gel eluting with dichloromethane to give 3-morpholino-2-nitrotoluene (124 g; m.pt. 85-90°C) as a yellow/orange solid.

b) A solution of 3-morpholino-2-nitrotoluene (72.4 g; see 8 (a) above) in dry toluene (500 ml) was hydrogenated in a large pressure vessel using palladium on charcoal (10% 4 g). The hydrogen pressure was kept at 3.9 bar for 4 hours. The resulting mixture was filtered through diatomaceous earth (available under the trade name "Celite") and the filter pad was washed with toluene (1 x 100 ml). The combined toluene solutions were evaporated to dryness and the residue was washed with petroleum ether (bp 60-80°C, 200 ml) and dried in vacuo at 40°C to give a pink solid (56.6 g). 5g of this solid was recrystallised from petroleum ether (bp 60-80°C) to give a pale pink solid which was dried in vacuo at 50°C to give 6-methyl-2-morpholinoaniline (4.1 g, m.pt. 83-86°C).

c) A solution of 6-methyl-2-morpholinoaniline (44.6 g; see 8 (b) above) and methyl isothiocyanate (24 g) in dichloromethane (325 ml) was stirred at ambient temperature for 4 days. The resulting mixture was evaporated to give a pale yellow solid which was washed with petroleum ether (bp 60-80°C, 400 ml) to give an off-white solid which was dried in vacuo at 70°C to give N-methyl-N'-(6-methyl-2-morpholinophenyl)thiourea (58.2 g; m.pt. 174-177°C).

d) A mixture of N-methyl-N'-(6-methyl-2-morpholinophenyl)thiourea (58.2 g; see 8 (c) above), methyl iodide (34.4 g) and dry acetone (500 ml) was stirred and refluxed for 4½ hours to give a solution. The acetone was distilled off and the resulting solid was ground up, washed with petroleum ether (bp 60-80°C; 400 ml) and dried in vacuo to give 2-methyl-1-(6-methyl-2-morpholinophenyl)-3-methyl-2-thiopseudourea hydroiodide (89.8 g; m.pt. 180-184°C) as a white solid.

e) A mixture of 2-methyl-1-(6-methyl-2-morpholinophenyl)-3-methyl-2-thiopseudourea hydroidide (20 g; see 8 (d) above); pentylamine (8.6 g, 11.4 ml), absolute ethanol (68 ml) potassium hydroxide (2.5 g) and lead (II) acetate trihydrate (8.5 g) was stirred at reflux for 20 hours. More pentylamine (5.7 ml), ethanol (34 ml), potassium hydroxide (1.25 g) and lead (II) acetate trihydrate (4.25 g) were added and the resulting mixture was stirred at reflux for a further 24 hours. The solvent was distilled off and water (120 ml) and dichloromethane (120 ml) were added. The mixture was stirred for 10 minutes, and then filtered through diatomaceous earth (available under the trade name "Celite"). The filter pad was washed with dichloromethane (3 x 150 ml). The dichloromethane phase was separated off, dried over magnesium sulphate, filtered and then evaporated to give a yellow oil. An attempt to make the fumarate salt at this stage failed. The free base was liberated again by basification and dissolved in dichloromethane (200 ml). The resulting mixture was extracted into 3M hydrochloric acid (2 x 150 ml) and the acidic aqueous phase was backwashed with dichloromethane (1 x 150 ml). The acidic aqueous phase was then basified to pH 14 with 5M aqueous sodium hydroxide solution and extracted with dichloromethane (2 x 200 ml). The extracts were dried over magnesium sulphate, filtered and evaporated to give a yellow oil. This oil was mixed with fumaric acid (5.8 g) and ethanol (100 ml) and the resulting mixture was refluxed for 1 hour to give a solution. Diethyl ether (400 ml) was added and a gum precipitated. The gum was washed several times with diethyl ether (3 x 100 ml) to give a gummy solid, which was recrystallised from ethanol (50 ml) and diethyl ether (200 ml) and the resulting solid was washed with more ether (3 x 100 ml) to give a white solid which was dried <u>in vacuo</u> at 60°C to give <u>N</u>-methyl-<u>N</u>′-[6-methyl-2-

morpholinophenyl]-N''-pentylguanidine monofumarate (15.8 g; m.pt. 147-149°C).

Example 9

A mixture of 2-methyl-1-(6-methyl-2-morpholinophenyl)-3-methyl-2-thiopseudourea thiopseudourea hydroiodide (13.0 g; see example 10 (d) above), N-methylbutylamine (8.6 g), absolute ethanol (45 ml), potassium hydroxide (1.63 g) and lead (II) acetate trihydrate (5.6 g) was stirred and refluxed for 23 hours. More N-methylbutylamine (5.8 ml), potassium hydroxide (0.8 g) lead (II) acetate trihydrate (2.75 g) and ethanol (30 ml) were added and the resulting mixture was refluxed for another 24 hours. The ethanol was distilled off and water (100 ml) was added to the residue. Dichloromethane (100 ml) was then added and the resulting mixture was stirred for 15 minutes and then filtered through diatomaceous earth (available under the trade name "Celite"). The residue was washed with dichloromethane (3 x 100 ml). The dichloromethane phases were separated off, combined and extracted into 3M hydrochloric acid (2 x 150 ml). The acid phase was backwashed with dichloromethane (1 x 100 ml) and then basified to pH 14 with aqueous sodium hydroxide solution (15M). The basic aqueous phase was then extracted with dichloromethane (4 x 100 ml) and the extracts were dried over magnesium sulphate, filtered and then evaporated to give a clear oil. The fumarate salt was prepared by refluxing this oil with fumaric acid (3.1 g) and ethanol (70 ml) for 1 hour and then adding diethyl ether (300 ml) and cooling to 0°C. The resulting solid was filtered off, washed with diethyl ether (30 ml) and dried in vacuo at 60°C to give N-butyl-N,N''-dimethyl-N'-[6-methyl-2-

morpholinophenyl]guanidine monofumarate (7.15 g; m.pt. 169-172°C).

Example 10

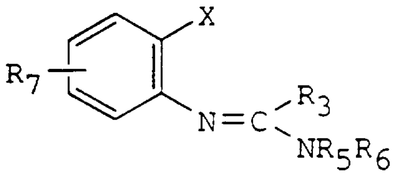
a) 6-Methyl-2-morpholinoaniline (10.81 g; see example 8 (b) above) was heated with butyl isothiocyanate (6.47 g) in dry dichloromethane (120 ml) with boiling under reflux for a total of 12 hours. The resulting mixture was distilled to dryness to give N-butyl-N'-(2-methyl-6-morpholinophenyl)thiourea.

b) N-Butyl-N'-(2-methyl-6-morpholinophenyl)thiourea (17.28 g; see 10 (a) above) and methyl iodide (3.85 ml) were heated together in acetone (140 ml) with boiling under reflux for 3¼ hours. The resulting mixture was then evaporated to dryness. The crude product was triturated with petroleum ether (b.pt. 40-60°C; 200 ml) and then purified by flash chromatography on silica gel eluting with dichloromethane/methanol (99:1-95:5) to give 3-butyl-2-methyl-1-(2-methyl-6-morpholinophenyl)-2-thiopseudourea hydroiodide (16.38 g; m.pt. 60°C).

c) A mixture of 3-butyl-2-methyl-1-(2-methyl-6-morpholinophenyl)-2-thiopseudourea hydroiodide (16.1 g; see 10 (b) above) and 5.6 molar dimethylamine in ethanol (60 ml) were boiled under reflux for 24 hours. More dimethylamine solution (60 ml) was added and the resulting mixture was stirred at ambient temperature for 24 hours. More dimethylamine (60 ml) was added and stirring was continued for 95 hours. Lead (II) acetate (13.6 g) and potassium hydroxide (2 g) were added and the resulting mixture was stirred for 72 hours. More dimethylamine (60 ml) was added and the resulting mixture was boiled under reflux for a total of 14 hours. The ethanol was distilled off, water (100 ml) and dichloromethane (100 ml) were added and the resulting mixture was filtered through diatomaceous earth (available under the trade name "Celite") washing the filter pad with more water (100 ml) and dichloromethane (100 ml). The mixture was separated and the dichloromethane solution was extracted with 3M hydrochloric acid (2 x 100 ml) and the combined acid phase was washed with dichloromethane (150 ml). The acid phase was basified with 5M aqueous sodium hydroxide solution and extracted with dichloromethane (3 x 150 ml). The combined, dried basic extracts were dried over magnesium sulphate and then distilled to dryness to give a crude product. The crude product (6.12 g) was dissolved in absolute ethanol (approximately 150 ml) and boiled with fumaric acid (2.23 g) in absolute ethanol (approximately 100 ml) for 1¼ hours. The cooled solution was added dropwise to stirred diethyl ether (800 ml) and filtered to give N-butyl-N′,N′-dimethyl-N′′-(2-methyl-6-morpholinophenyl)guanidine (6.8 g; m.pt. 195-196°C).

Claims

1. A method for the treatment and/or prevention of cerebral and/or cardiac ischaemia, convulsion and/or sickle cell anaemia in which a therapeutically effective amount of a compound of formula I

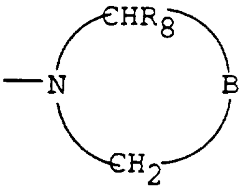


I

or a pharmaceutically acceptable salt thereof is administered to a mammal in need of such treatment in conjunction with a pharmaceutically acceptable diluent or carrier,

in which X is H, nitro, cyano, halo, phenyl (optionally substituted by halo and/or alkyl containing 1 to 3 carbon atoms and/or alkoxy containing 1 to 3 carbon atoms or alkanoyl containing 2 to 4 carbon atoms, or a group of formula $S(O)_mR'$ wherein m is 0 or 1 or 2 and R' is an alkyl group containing 1 to 3 carbon atoms) an alkyl group containing 1 to 4 carbon atoms or a group of formula $-(CH_2)_n\ NR_1R_2$

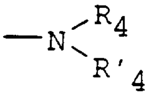
in which n is 0 or 1 and R_1 and R_2, which are the same or different, are (a) an aliphatic group containing 1 to 3 carbon atoms, said aliphatic group being optionally substituted by methoxy (b) a cycloalkyl group containing 3 to 7 carbon atoms or (c) R_1 and R_2 together with the nitrogen atom to which they are attached form an optionally substituted heterocyclic ring of formula II



II

in which R_8 represents H or an alkyl group containing 1 to 3 carbon atoms and B represents an alkylene group of 2 to 4 carbon atoms optionally interrupted by oxygen, sulphur, sulphinyl or nitrogen optionally substituted by an alkyl group containing 1 to 3 carbon atoms, said alkylene group being optionally substituted by one or more alkyl groups containing 1 to 3 carbon atoms or the substituents on two adjacent carbon atoms of the alkylene group form a benzene ring or B represents an alkenylene group of 3 carbon atoms;

R_3 is a straight or branched alkyl group containing 1 to 7 carbon atoms or a guanidine group (optionally N-substituted in both the 1 and 3 positions with one or two alkyl groups containing 1 to 3 carbon atoms) or R_3 is a cycloalkyl group containing 3 to 7 carbon atoms or a group of formula III



$$-N\begin{matrix}\diagup R_4 \\ \diagdown R'_4\end{matrix}$$

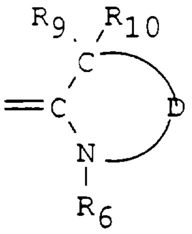
III

in which R_4 and R'_4, which are the same or different, are H or an alkyl group containing 1 to 4 carbon atoms;

R_5 is H or a straight or branched aliphatic group of 1 to 4 carbon atoms, said aliphatic group being optionally substituted by methoxy;

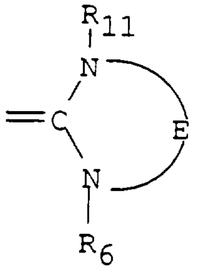
R_6 is (a) H, or phenyl (optionally substituted by halo and/or alkyl containing 1 to 4 carbon atoms and/or alkoxy containing 1 to 4 carbon atoms) (b) a straight or branched aliphatic group of 1 to 6 carbon atoms optionally substituted by hydroxy or an acylated derivative thereof, by an alkoxy group containing 1 to 3 carbon atoms, by an alkylthio group containing 1 to 3 carbon atoms, by an optionally alkylated amino group, by a carbocyclic group containing 3 to 7 carbon atoms, by pyridyl or by cyano or (c) a cycloalkyl ring containing 3 to 7 carbon atoms and optionally substituted by hydroxy;

or the group R_3 and the group R_5 together with the carbon and nitrogen atoms to which they are attached form a heterocyclic ring of formula IV



in which R_6 is as hereinbefore defined, R_9 and R_{10}, which are the same or different, are H or an alkyl group of 1 to 4 carbon atoms optionally substituted by methoxy and D is an oxyethylene group in which the oxygen atom is bonded to the carbon atom carrying the groups R_9 and R_{10} or an alkylene group of 2 to 5 carbon atoms optionally substituted by one or more alkyl groups of 1 to 3 carbon atoms;

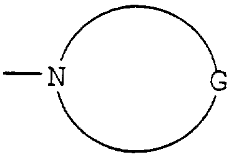
or the group R_3 and the group R_5 together with the carbon and nitrogen atoms to which they are attached form a heterocyclic ring of formula V



V

in which R_6 is as hereinbefore described, R_{11} is H or an alkyl group containing 1 or 2 carbon atoms, and E is an alkylene group of 2 to 4 carbon atoms optionally substituted by one or more alkyl groups containing 1 to 3 carbon atoms;

or R_5 and R_6 together with the nitrogen atom to which they are attached form a heterocyclic ring of formula VI



VI

in which G is an alkylene or alkenylene group of 4 to 6 carbon atoms optionally interrupted by oxygen, sulphur, sulphinyl, sulphonyl, or nitrogen said nitrogen being optionally substituted by (a) a carbocyclic ring containing 3 to 7 carbon atoms (b) a methylsulphonyl group or (c) an alkyl group containing 1 to 3 carbon atoms and optionally substituted by hydroxy or an alkoxy group containing 1 to 3 carbon atoms; said alkylene group being optionally substituted by (a) one or more alkyl groups containing 1 to 3 carbon atoms and optionally substituted by hydroxy, (b) by one or more hydroxy groups or an ester thereof, (c) by one or more alkoxy groups containing 1 to 3 carbon atoms, (d) by oxo or a derivative thereof (eg an oxime or oxime ether) (e) by dimethylcarbamoyl or (f) by one or more groups of formula $S(O)_pR''$ in which p = 0 or 1 or 2 and R'' is an alkyl group containing 1 to 3 carbon atoms; and

R_7 represents H or a group of formula II above or one or more optional substituents selected from halo, alkyl groups containing 1 to 4 carbon atoms optionally substituted by methylthio, alkoxy groups containing 1 to 3 carbon atoms, alkylthio groups containing 1 to 3 carbon atoms, alkylsulphinyl groups containing 1 to 3 carbon atoms, alkylsulphonyl groups containing 1 to 3 carbon atoms, alkoxycarbonyl groups containing a total of 2 or 3 carbon atoms, trifluoromethyl or cyano.

2. The use of a compound of formula I as defined in claim 1 in the manufacture of a medicament for the treatment and/or prevention of cerebral and/or cardiac ischaemia.

3. The use of a compound of formula I as defined in claim 1 in the manufacture of a medicament for the treatment and/or prevention of sickle cell anaemia.

4. The use of a compound of formula I as defined in claim 1 in the manufacture of a medicament for use as an anticonvulsant.

5. The use of a compound of formula I as defined in claim 1 in the manufacture of a medicament for use as a neuroprotective agent (ie for the treatment and/or prevention of neurological disorders).

6. A pharmaceutical composition for the treatment and/or prevention of cerebral and/or cardiac ischaemia comprising a therapeutically effective amount of a compound of formula I as defined in claim 1 in

conjunction with a pharmaceutically acceptable diluent or carrier.

7. A pharmaceutical composition for the treatment and/or prevention of sickle cell anaemia comprising a therapeutically effective amount of a compound of formula I as defined in claim 1 in conjunction with a pharmaceutically acceptable diluent or carrier.

8. A pharmaceutical composition for use as an anticonvulsant comprising a therapeutically effective amount of a compound of formula I as defined in claim 1 in conjunction with a pharmaceutically acceptable diluent or carrier.

9. A compound of formula I selected from:

N-butyl-N'-(2-fluoro-6-morpholinophenyl)-N''-methylguanidine;
N-butyl-N'-(2,6-dimorpholinophenyl)-N''-methylguanidine;
N-butyl-N'-methyl-N''-[2-methyl-6-(perhydro-4H-1,4-thiazin-4-yl)phenyl]guanidine;
N-butyl-N'-methyl-N''-(2-methyl-6-piperidinophenyl)guanidine;
N-butyl-N'-methyl-N''-(2-methyl-6-morpholinomethylphenyl)guanidine;
N-butyl-N'-methyl-N''-(3-methylbiphenyl-2-yl)guanidine;
N-butyl-N'-methyl-N''-(2-tolyl)guanidine;
N-methyl-N'-[6-methyl-2-morpholinophenyl]-N''-pentylguanidine;
N-butyl-N,N''-dimethyl-N'-[6-methyl-2-morpholinophenyl]guanidine;
N-butyl-N',N'-dimethyl-N''-(2-methyl-6-morpholinophenyl)guanidine;

and pharmaceutically acceptable salts thereof.

10. A pharmaceutical composition comprising an active substance and at least one pharmaceutically acceptable diluent or carrier, characterised in that as active substance it comprises a compound of formula I as claimed in claim 9 in a therapuetically effective amount.

11. The use of a compound of formula I as claimed in claim 9 as a neuroprotective agent and/or for the treatment and/or prevention of cerebral and/or cardiac ischaemia, convulsion and/or sickle cell anaemia.

INTERNATIONAL SEARCH REPORT

Interna al Application No
PCT/EP 95/04673

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/535 A61K31/415 A61K31/445 A61K31/495 A61K31/40
A61K31/155

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,92 00273 (BOOTS CO PLC) 9 January 1992 cited in the application see the whole document ---	1-11
A	EP,A,0 385 038 (BOOTS CO PLC) 5 September 1990 cited in the application see the whole document --- -/--	1-11

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search 3 April 1996	Date of mailing of the international search report 19. 04. 96
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Mair, J

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INTERNATIONAL SEARCH REPORT

Interna ·al Application No
PCT/EP 95/04673

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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A	JOURNAL OF MEDICINAL CHEMISTRY, vol. 18, no. 1, 1975 pages 90-99, JEN, T. ET AL 'Amidines and related compounds. 6. Studies on structure-activity relationships of antihypertensives and antisecretory agents related to clonidine' see the whole document ---	9-11
A	JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 97, no. 10, 1975 pages 2811-2818, JACKMAN, L.M. ET AL '1H and 13C nuclear magnetic resonnance studies on the tautomerism, geometrical isomerism and conformation of some cyclic amidines, guanidines and related systems' see the whole document especially page 2818, table IX, compounds 43,44 & 45 ---	9
A	EP,A,0 310 410 (KAWATE, TSUNEYOSHI) 5 April 1989 see the whole document -----	1-11

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